

Understanding Clinical and Patient Reported Response of Children and Young People with Cerebral Palsy to Botulinum Toxin A: A Longitudinal Observational Study (The Toxin Study)



Lesley R Katchburian

University College London Great Ormond Street Institute of Child Health

A thesis submitted for the degree of Doctorate of Philosophy

This research was funded by an NIHR ICA-CDRF-2015-01-037

July 2022

Students Declaration

I Lesley Katchburian confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I can confirm that this has been indicated in the thesis.

Date: 29th July 2022

Research Team

Researcher and PhD candidate

Lesley Katchburian (LK)

Academic Supervisory Team

Professor Eleanor Main

Dr Kate Oulton (KO)

Professor Jo Wray

Expert Advice and Clinical Supervisor

Dr Lucinda Carr (LC)

Statistical Supervisor

Dr Eirini Koutoumanou

Collaborator and PPIE Supervisor

Professor Christopher Morris

Collaborators

Professor Roslyn Boyd

Professor Virginia Wright

Expert Advice

Dr Belinda Crowe (BC)

Acknowledgements

A PhD is an enormous undertaking and a journey that is not possible to take alone. I have been absolutely privileged with the support of many people during my PhD journey over the last six years. I would like to offer my gratitude to all who have enabled my personal and intellectual growth, provided financial and practical support, and have enriched my life during this period.

My supervisory team has been outstanding. I would like to say a huge thank you to my academic supervisors, Professor Eleanor Main, Dr Kate Oulton and Professor Jo Wray, who have all brought such different perspectives, guiding me and supporting my development as a clinical academic as well as providing endless encouragement to keep going. I would also like to especially thank Dr Lucinda Carr, who has been there for me from the very beginning, providing me with the encouragement to begin this work and inspiring me both as my clinical supervisor and long time mentor.

I would like to thank Dr Eirini Koutoumanou for her expert guidance with the statistical work for this research and for her endless patience. Also my collaborators Professors Virginia Wright, Christopher Morris and Roslyn Boyd, through you all I have learnt so much.

I am enormously grateful to all the children, young people and their families who took part in this study and generously gave their time to participate in this research. You ultimately made this happen, thank you for taking the time to share your experiences with such enthusiasm over the 12 months.

Heartfelt thanks go to the outstanding Movement Disorders Team at GOSH, especially, Stephanie Cawker, Dr Belinda Crowe, Xanthe Hodgson, Emile Hupin, Katharine Phillipps, Agnieszka Rozborska, Josie Scerri and the rest of the multidisciplinary team. Thank you, without your support and continued input this study would never have happened.

I am blessed to have such a supportive family and I am eternally grateful to my husband Marcos for his unfailing support and encouragement throughout this doctorate. Thank you to my sons, Alessandro and Luca whose interest in my work and constant encouragement has kept me going. I am so proud of the incredible young men you have become during the six years of my PhD. Ultimately, I must thank my incredible parents, John and Maureen Rice and all my family for their endless support and never ending belief in me.

Finally, I would like to express my thanks to the National Institute for Health Research and Health Education England for this Clinical Doctoral Research Fellowship, which made this research possible.

Abstract

Background

Botulinum Toxin A (BoNT-A) is an established treatment for focal spasticity in children and young people with spastic cerebral palsy (CYPwCP). A systematic review of the available literature within this thesis highlighted that the published evidence for BoNT-A effectiveness is mostly related to short term outcomes focused on impairment level, relating to restriction of body functions and structures, rather than more meaningful measures of activity and participation.

Aims

To determine the effect of lower limb BoNT-A on ambulant CYPwCP by evaluating outcome across the WHO's International Classification of Functioning and Disability (ICF) domains of body structure and function, activity and participation and change in movement quality over a 12-month period and investigate whether clinical outcomes reflect children and families' experience of BoNT-A treatment.

Method

A prospective observational mixed methods longitudinal study used a one group repeated measures design conducted in two phases. In Phase I the Quality Function Measure and the Canadian Occupational Performance Measure were used to evaluate change in movement quality and evaluate goal attainment following lower limb BoNT-A treatment. Change was also evaluated throughout the ICF domains of body structure and function, activity and participation, using a number of secondary outcome measures (64 CYPwCP). In Phase II semi-structured interviews with a subgroup of families from Phase I explored CYPwCP and parents experience of BoNT-A treatment (Phase II: 18 CYPwCP).

Results

There was a significant improvement in movement quality and goal attainment across the 12 months following BoNT-A. Spasticity was significantly reduced at 6 weeks with mixed results at 6 and 12 months, dependent on the muscles injected.

Functional balance and gait improvements, although improved at 6 weeks, only reached clinical significance at 6 and 12 months, respectively. However, clinically significant improvement in motor function and participation outcomes were seen at 6 weeks post BoNT-A and these were maintained across 12 months. CYPwCP and their families described improvements in movement quality and short term reduced stiffness following injections which were associated with increased activity, improved participation opportunities and increased confidence and self esteem.

Conclusion

The findings from this study suggest that judicious, targeted use of BoNT-A does have a place in improving activity and participation for CYPwCP. Although improvement in impairment measures were clinically significant up to six months following treatment, the improvement in activity, participation and quality of life associated with goal attainment following treatment were maintained for up to 12 months following treatment. The findings suggest that re-injection intervals of up to 12 months should be considered in clinical practice. Outcome should be evaluated past the short-term post injection period of 6-12 weeks and beyond a change in impairment in order to assess the effectiveness of BoNT-A in successfully 'improving functioning and participation', which was the main driver for families seeking treatment.

Statement of Impact

'If an intervention fails to enhance the quality of life, activity or participation for that child or family either in the short or long term, is it justifiable?'

(Damiano et al., 2021)

The use of Botulinum Toxin A (BoNT-A) to treat muscle stiffness (spasticity) is well established in children and young people with cerebral palsy (CYPwCP) but there are concerns that BoNT-A may be over prescribed. The long-term effect of repeated injections on growing muscle is as yet unknown, with some research suggesting potential harm from excessive treatment episodes. It is essential to optimise BoNT-A use by targeting treatment to the right children at the right time for the right length of time, with appropriate intervals between treatments.

Unlike other studies which have focused only on change at an impairment level such as muscle stiffness following BoNT-A, this research has illustrated the importance of measuring change in areas that are important to children and their families such as activity and participation

The significant amount of data presented highlights the depth and breadth of this study, reflecting true clinical practice. This work has potential benefits for CYPwCP, their families and clinicians, with a number of implications for clinical practice.

The results of this pragmatic study indicated that lower limb BoNT-A injections significantly improved activity and participation in CYPwCP. Changes in ICF body structure and function outcomes suggested short- and medium-term improvement (up to 6 months) following BoNT-A injections, while changes in a child's movement quality, activity, participation and health related quality of life outcomes appeared to show more lasting improvement over 12 months. This was accompanied by significant improvement in goal attainment across the 12 months following BoNT-A treatment.

Results have highlighted that it is essential to consider change in activity and participation outcomes as well as change in impairment, if unnecessary injection episodes are to be avoided. Decision making regarding re-injection based on impairment alone could result in shorter re-injection intervals, when improvement in activity and participation, the main drivers for parents and children seeking treatment, may well still be evident.

This research recommends that judicious use of BoNT-A requires routine standardised evaluation of impact on quality of life, activity and participation following treatment in order to optimise care and avoid unnecessary treatment.

Academic output

The following is a summary of the work and achievements during this doctorate.

Peer-reviewed journal articles

Katchburian L, Oulton K, Main E, Morris C, Carr L, (2021) 'Protocol for The Toxin Study: Understanding clinical and patient reported response of children and young people with cerebral palsy to intramuscular lower limb Botulinum neurotoxin-A injections, exploring all domains of the ICF. A pragmatic longitudinal observational study using a prospective one-group repeated measures design' *BMJ Open* 2021;**11**:e049542. doi: 10.1136/bmjopen-2021-049542 (Appendix 14.11)

Katchburian L (2022) A clinical commentary on the 'Development of the Gross Motor Function Family Report (GMF-FR) for Children with Cerebral Palsy', *Physiotherapy Canada* (Physiotherapy Canada 2023 75:1, 92-93)

Conference Poster presentations

Katchburian L, Hodgson X, Hupin E, Philipps K, Rosborzka A, Scerri J (2019) 'Use of the Quality Function Measure to evaluate changes in the quality of movement in ambulant children with cerebral palsy following lower limb botulinum neurotoxin A injections.' 31st Annual Meeting European Academy of Childhood Disability, Paris, France. *Dev Med Child Neurol*, 61: 62-82. doi:10.1111/dmcn.14245. Awarded DMCN Best Poster (Appendix 14.11)

Chugh D, Morgan S, Cawker S, **Katchburian L**, Carr L, Aquilina K (2019) 'Use of the Quality Function measure to determine changes in the quality of movement in ambulant children with CP after Selective Dorsal Rhizotomy.' Presented at the 31st Annual Meeting European Academy of Childhood Disability, Paris, France May 2019.

Geronta I, Davenport S, **Katchburian L** (2019) 'Using the Modified Tardieu Test to predict outcome of Botulinum Toxin A injections in the lower limb of ambulant children with CP' Presented at the 31st Annual Meeting European Academy of Childhood Disability, Paris, France, May 2019.

Livermore P, Bichard E, Brind J, Handley S, Harniess P, **Katchburian L**, et al., (2020) 'The importance of peer-support for clinical academics in a children's hospital' *Archives of Disease in Childhood* 2020;105:A24.

Murray L, Coghill J, **Katchburian L** (2021) 'Systemic adverse events and side effects following intramuscular Botulinum Toxin A in children with cerebral palsy and movement disorders' *Archives of Disease in Childhood* 2021;**106**:A490

Crowe B, **Katchburian L**, Hodgson X, Hardy C. (2021) 'Digitising an integrated care pathway to deliver consistent high-quality clinical care for Botulinum Toxin A use in cerebral palsy' *Archives of Disease in Childhood* 2021;**106**:A37.

Katchburian L, Kleiner A, Crowe B, Hodgson X, Carr L, Main E (2022) 'Use of the Modified Tardieu Scale in the assessment of dynamic spasticity in children with ambulant cerebral palsy' *Dev Med Child Neurol*, 64 suppl 2: 5-107. (Appendix 14.11)

Katchburian, L, Fielding, N., Hodgson, X., Carr,L, Crowe,B., Oulton,K., Morris,C., Wray,J., Main,E (2022) 'The effects of lower limb Botulinum neurotoxin-A injections on goal-directed outcomes in ambulant children with cerebral palsy' *Dev Med Child Neurol*, 64 suppl 2: 5-107. (Appendix 14.11)

Katchburian,L, Hodgson,X.,Crowe,B.,Oulton,K. Morris,C, Wray,J.,Main,E. Carr,L (2022) 'Use of the Quality Function Measure (QFM) to evaluate quality of movement in ambulant children with cerebral palsy following lower limb Botulinum Toxin A (BoNT-A) injections' *Dev Med Child Neurol*, 64 suppl 2: 5-107. (Appendix 14.11)

Manuscripts awaiting publication

Chugh D, Cawker L, **Katchburian L**, Carr L, Aquilina K. (2023) 'Quality of Movement Changes in ambulatory children with cerebral palsy: one year after single level Selective Dorsal Rhizotomy' (Manuscript submitted for publication).

Katchburian L, Wray J, Oulton K, Main E, Carr L. (2023) Do lower limb Botulinum Toxin A injections have an impact on impairment, activity limitation and participation restriction in ambulant children (GMFCS I-III) with Cerebral Palsy? A systematic review across the ICF domains (manuscript in preparation).

Conference Presentations-Invited talks and workshops

Katchburian L 'Understanding the role of Botulinum Toxin A in cerebral palsy- are we measuring what is important to children and families?' Spotlight on AHP translational research, UCL, London, May 2016.

Katchburian L. 'My NIHR Research Journey...Academic Clinician or Clinical Academic?' Paediatric Clinical Academics, NIHR Biomedical Research Centre, UCL Institute of Child Health National Residential Conference, Ashridge Business School, 1-2nd October 2016.

Katchburian L. 'Evaluating Botulinum Toxin use in cerebral palsy are we using the right outcomes?' Paediatric Research Group, UCLGOSICH, March 2017.

Katchburian L. 'The use of the Quality Function Measure to evaluate change following interventions in cerebral palsy', Cork, Ireland, May 2017.

Katchburian L. 'Implementing a clinical study to evaluate outcome following BoNT-A use in CP', Pan-London Neurodisability Group Study Day, Great Ormond Street Hospital, London, August 2017.

Katchburian L. 'Understanding the role of Botulinum Toxin A in cerebral palsy- are we measuring what is important to children and families?' Association of Paediatric Chartered Physiotherapists AGM, London, October 2017.

Katchburian L. 'The role of the non-medical injector in the use of Botulinum Toxin in cerebral palsy'. Queensland Children's Hospital, Brisbane, Australia, March 2018.

Katchburian L. 'Management of Motor Disorders with Botulinum Toxin A: An update on current Research', Cambridge, October 2018.

Katchburian L. 'The management of motor disorders with Botulinum Toxin A: Where are we now?' Clinical Governance Conference, Kent, November 2018.

Katchburian L. 'The use of Botulinum Toxin A in the management of movement disorders', Association of Paediatric Chartered Physiotherapists, London, April 2019.

Katchburian L. 'Management of Motor Disorders with Botulinum Toxin A - current evidence', Paediatric conference, West Suffolk, England, May 2019.

Katchburian L. 'UK model of Tone Management- sharing practice'. Collaborative meeting of AHP researchers, Hong Kong Children's Hospital, Hong Kong, May 2019.

Katchburian L. 'National Research Priority Setting workshop- Identifying AHP research in the paediatric neurodisability setting', British Academy of Childhood Disability Strategic Research Group, (Facilitator), Chartered Society of Physiotherapists, London, September 2019.

Katchburian L. 'The role of the non-medical injector in the use of Botulinum Toxin in cerebral palsy', Inaugural meeting of UK Paediatric Neurotoxin Network, Lady Margaret Hall, Oxford, September 2019.

Katchburian L. 'Management of motor disorders with botulinum toxin A: Update on current research', British Bobath Association AGM, Derby, February, 2020.

Katchburian L. 'Impact of Covid-19 on service delivery', Paediatric British Neurotoxin Network, June 2020 (Virtual presentation).

Katchburian L., Hodgson X. 'Management of motor disorders with botulinum toxin A -current evidence & service delivery', Great Ormond Street Hospital, August 2020 (Virtual presentation).

Katchburian L., Carr L, Cawker S. 'Medical & surgical management of motor disorders', UCL November 2020 (Virtual presentation).

Katchburian L. 'Toxin in the time of coronavirus – what's changed?' Leaders in Neuroscience Series: Paediatric Toxin Management during Covid-19, September 2020 (Virtual conference)

Katchburian L. 'The paediatric perspective' – panellist. BNN annual meeting – Covid edition, September 2020 (Virtual conference).

Katchburian L., Carr L. 'Current thinking about dosage and frequency of injections in paediatric practice', Annual Meeting pBNN, September 2020 (Virtual conference)

Katchburian L. 'Management of motor disorders with botulinum toxin A: Update on current research', 4th International Conference on Paediatric Spasticity, Orthopaedic and Postural Management, Cork, Ireland, November 2020 (conference cancelled).

Katchburian L. 'Management of motor disorders with botulinum toxin A: An update on current research', Cerebral Palsy 'Interventions and Best Practice' Virtual Webinar World CP Day, International Association of Paediatric Neurology, Kerala, India October 2021.

Katchburian L. 'Use of Botulinum Toxin A and Goal attainment in Cerebral Palsy', BNN Annual meeting, Queens College, Oxford, September 2021.

Katchburian L, Cawker S, Carr L. 'Current thinking about Management of Motor Disorders- what is the evidence?' Great Ormond Institute of Child Health UCL, November 2021

Katchburian L, Cawker S, Scerri J, Crowe B. 'The use of Ultrasound in Botulinum Toxin A administration in cerebral palsy' (workshop), British Society for children's orthopaedics Annual Meeting, Surrey, 10-11th March 2022

Katchburian L, 'Understanding the use of intramuscular Botulinum Toxin A in ambulant children with cerebral palsy', Inaugural Physiotherapy Research Symposium, Great Ormond Institute of Child Health UCL, London, May 2022

Katchburian L. 'The Role of Botulinum Toxin A in the management of increased tone', Annual Paediatric Neurology Forum, Royal London Hospital, London, June 2022

Katchburian L 'The role of Botulinum Toxin A injections in improving activity, participation and health related quality of life in ambulant children with cerebral palsy', Paediatric Neurology Study Day, Chailey Clinical Services, Sussex, July 2022

Katchburian L 'The role of Botulinum Toxin A injections in improving activity, participation and health related quality of life in ambulant children with cerebral palsy', Great Ormond Street Hospital, London, July 2022

Awards

'Early Career Researcher Award' awarded in 2018 by the Centre for Outcomes and Experience Research in Children's Health Illness and Disability (ORCHID)/NIHR GOSH Biomedical Research Centre

'Best Posters Award' awarded by Developmental and Child Neurology at EACD conference, Paris 2019

'Early Career Researcher Travel Award' awarded in 2018 and 2019 by ORCHID/NIHR GOSH Biomedical Research Centre.

These were used for two International visits and collaborations:

March 2018, visit to the Queensland Cerebral Palsy and Rehabilitation Research Centre (QCPRRC) in Australia which was established to improve health outcomes for children with cerebral palsy and is linked to Queensland's Children's Hospital.

May 2019, visit to the Movement Disorders Service of Hong Kong Children's Hospital, Kowloon City, the first public children's hospital in Hong Kong. Both visits have resulted in ongoing collaborations with the teams from these centres.

Clinical Academic achievements

Since starting my clinical doctoral research fellowship In 2016, I have continued with my clinical academic career, combining clinical work at GOSH in the Movement Disorders Service, in addition to contributing to national professional groups and teaching and mentoring clinicians within the neurodisability field.

In 2018, I was elected the physiotherapy representative on the strategic research group (SRG) of the British Academy of Childhood Disability. The SRG is responsible for advising on research policy at a national level and works closely with the NIHR to further neurodisability research.

In 2020, I was elected to the National Board of Directors for the Paediatric British Neurotoxin Network. This is a multidisciplinary network which aims to establish consensus and promote best practice of the use of BoNT-A both in paediatric and adult services.

In 2021, I was recognised for my clinical academic contribution to my professional community and was honoured to be awarded Fellowship of the Association of Paediatric Chartered Physiotherapists (APCP).

I am keen to encourage research in the clinical setting and have been pleased to showcase this work, using a variety of different mediums. These have included highlighting the role of the clinical academic researcher on the Paul O'Grady TV show filmed at GOSH (<https://www.gosh.nhs.uk/news/my-path-research-meet-gosh-physiotherapist-lesley/>). As well as being part of the AHP research champion national campaign for the NIHR, encouraging AHPs to carry out research in the clinical setting (<https://t.co/AEGo8x3uyA>).

During my PhD thesis, I have supervised four MSc students to successful completion and mentored several other therapists during their MSc studies. I have continued to teach on the MSc Postgraduate programme at UCL GOSICH and have been invited to be a clinical academic supervisor on three NIHR CDRF applications and two PCAF applications to date. I am eager to continue the work of a clinical academic and look forward to supporting others on their future clinical academic journeys.

List of Abbreviations

3DGA	Three-dimensional gait analysis
AHP	Allied Health Professional
ANOVA	Analysis of variance
BoNT-A	Botulinum neurotoxin type-A
CI	Confidence interval
COPM	Canadian Occupational Performance Measure
CYPwCP	Children and young people with cerebral palsy
CP	Cerebral palsy
GAS	Goal attainment scaling
GDI	Gait Deviation Index
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GOSH	Great Ormond Street Hospital
GPS	Gait Profile Score
ICC	Intraclass correlation
ICF	International Classification of Functioning, Disability and Health
ICF-CY	International Classification of Functioning, Disability and Health: Children and Youth Version
IGA	Instrumented gait analysis
IQR	Interquartile range

MAS	Modified Ashworth Scale
MCID	Minimum clinically important difference
MDC	Minimum detectable change
MTS	Modified Tardieu Scale
OGS	Observational Gait Scale
PEDI	Paediatric Evaluation of Disability Inventory
ROM	Range of motion
PRS	Physicians Rating Scale
QFM	The Quality Function Measure
R&D	Research and Development
RCT	Randomised control trial
ROM	Range of motion
SD	Standard Deviation
SMC	Selective muscle control
SMS	Spasticity measurement system
SPSS	Statistical Package for Social Sciences
STS	Sit to stand
T0	Baseline Pre-injection
T1	Six weeks post-injection
T2	Six months post-injection
T3	Twelve months post injection
TUG	Timed up and go
VAS	Visual analogue scale
WHO	World Health Organization

TABLE OF CONTENTS

Declaration	2
Acknowledgements	4
Abstract	6
Statement of Impact	8
Academic Output	10
List of Abbreviations	16
Table of Contents	18
List of Figures	26
List of Tables	30
Chapter 1 Introduction	33
1.1.1 Introducing the researcher	33
1.1.2 Overview and context of the PhD	34
1.1.3 Aims and objectives of the PhD	35
1.1.4 Research Questions.....	36
1.1.5 Patient and public involvement and engagement (PPIE)	37
1.1.6 Thesis outline	38
1.2 Background.....	39
1.3 Cerebral Palsy	40
1.3.1 Classification of Cerebral Palsy	40
1.3.2 The Gross Motor Function Classification System (GMFCS)	42
1.3.3 The World Health Organization's International Classification of Functioning, Disability and Health -Children and Youth Model ICF-CY	43
1.4 Botulinum Neurotoxin -Type A (BoNT-A).....	45
1.4.1 BoNT-A- mechanism of action	45
1.4.2 Clinical use of intra-muscular Botulinum Toxin A (BoNT-A)	49

1.4.3	Effectiveness of BoNT-A in CP management	50
1.4.4	Optimal age for treatment.....	53
1.4.5	Re-injection interval.....	55
1.4.6	Physiological changes in muscle post BoNT-A toxin	57
1.4.7	Outcome measures and the ICF.....	59
1.5	Summary.....	62
Chapter 2	Systematic Review	65
2.1	Introduction and background.....	65
2.2	Method	66
2.2.1	Search Strategy	66
2.2.2	Data extraction, selection, and coding	70
2.3	Results	72
2.3.1	Data extraction.....	72
2.3.2	Participant and study characteristics.....	77
2.3.3	Methodological quality and adverse events.....	84
2.3.4	ICF Outcomes	87
2.3.5	Evaluation of Body function and structure	87
2.3.6	Evaluation of activity.....	94
2.3.7	Evaluation of participation.....	98
2.3.8	Health Related Quality of Life	99
2.3.9	Integration of the findings between the ICF domains.....	103
2.4	Discussion	106
2.4.1	Quality of evidence	106
2.4.2	Review findings within the ICF domains – short term versus long term change	107
2.4.3	Relating change between ICF domains.....	109

2.4.4	Outcome measures used in evaluating BoNT-A use in ambulant CYPwCP 110	
2.4.5	Variation within the review- population, previous treatment history and length of follow up.....	113
2.5	Strengths and Limitations.....	114
2.5.1	Strengths	114
2.5.2	Limitations.....	115
2.6	Conclusion and recommendations for future research	116
2.6.1	Future Research	117
Chapter 3	Research Outline	119
3.1	Aims and objectives of the PhD.....	119
3.2	Study design	120
3.3	Ethical considerations	122
3.3.1	Risks and burdens to participants.....	122
3.3.2	Potential benefits to participants	123
3.3.3	Confidentiality and Data Monitoring	123
3.3.4	Ethical approval.....	124
3.4	Study sample and setting	125
3.4.1	Sample size calculation	126
Chapter 4	Phase I – Quantitative study methodology.....	128
4.1	Study procedure and data collection	128
4.1.1	Recruitment	128
4.1.2	Validated outcome measures for all ICF domains	130
4.1.3	Training and fidelity	131
4.1.4	Data collection- clinical assessment	131
4.1.1	Administration of BoNT-A.....	132

4.2	Data collection- study outcome measures.....	133
4.2.1	Primary outcome measures	133
4.2.2	Secondary outcome measures.....	137
Chapter 5	Results Phase I: Participant demographics and BoNT-A treatment details	144
5.1	Sample and Recruitment	144
5.2	Demographics.....	148
5.2.1	BoNT-A treatment details of study participants	150
5.2.2	Treatment received within the study	157
5.3	Statistical analysis.....	157
Chapter 6	Results Phase I: Primary outcome measures.....	160
6.1	Quality Function Measure (QFM).....	160
6.1.1	QFM Analysis.....	162
6.1.2	QFM Descriptive Analysis.....	163
6.1.3	QFM Univariate analysis	166
6.1.4	QFM Attribute scores.....	168
6.1.5	QFM Administration.....	178
6.2	Canadian Occupational Performance Measure Analyses	186
6.2.1	COPM Scoring- An evaluation of averaged and total COPM goal scores	188
6.2.2	Comparison of averaged COPM Performance and Satisfaction scores between baseline and post BoNT-A intervention over twelve months.....	193
6.2.3	COPM Analyses using Individual Goal scores.....	200
Chapter 7	Results Phase I: Secondary Outcome Measures.....	211
7.1	Results	211
7.2	Body function and structure (BSF)	211
7.2.1	Measures of Spasticity and hypertonicity.....	212

7.2.2	Muscle selectivity- Selective Motor Control scale (SMC)	219
7.2.3	Pain - modified Faces Pain Scale (mFPS).....	220
7.3	Responders vs non responders for the study	223
7.3.1	Technical response – Results	225
7.4	Activity.....	229
7.4.1	TUG scores	230
7.4.2	1MFWT scores.....	233
7.4.3	GMFM -GMFM-66.....	235
7.5	Participation outcome measures	239
Chapter 8	Hierarchical Multilevel Regression model	243
8.1	Primary outcome measures	246
8.1.1	QFM.....	246
8.1.2	COPM	253
8.2	Secondary outcome measures	255
8.2.1	Body structure and Function.....	255
8.2.2	Activity.....	259
8.2.3	Participation	262
Chapter 9	Phase I Discussion	270
9.1	Body function and structure (BSF)	271
9.1.1	BSF Tone reduction	271
9.1.2	BSF Pain.....	274
9.2	Activity and QFM	276
9.3	Goal attainment following BoNT-A	279
9.3.1	Goal Type	282
9.3.2	Individual goal scores.....	283
9.4	Participation	285

9.5	Quality of life (QOL).....	288
9.6	Duration of response – re-injection interval.....	290
9.7	Age and repeated injection cycles	292
9.8	Safety.....	294
9.9	Strengths and Limitations.....	294
Chapter 10 Phase II- Qualitative study methodology.....		298
10.1	Introduction.....	298
10.2	Aim of the qualitative study	298
10.3	Design	299
10.4	Sample and recruitment.....	300
10.5	Semi-structured interview schedules.....	301
10.6	Data Analysis	305
Chapter 11 Results of Phase II		308
11.1	Phase II study demographics.....	308
11.2	Summary of the Thematic Analysis of Phase II interviews.....	310
11.3	Drivers for treatment	312
11.3.1	Managing pain and symptoms.....	312
11.3.2	Keeping up with peers	313
11.3.3	What have we got to lose?	318
11.4	Uncertainty about treatment Botulinum Toxin A.....	322
11.4.1	BoNT-A -The drug.....	324
11.4.2	BoNT-A -The injection procedure	328
11.4.3	BoNT-A -Timing and extent of the impact	329
11.5	Engagement- managing uncertainty and anxiety	331
11.5.1	Parental Engagement.....	332
11.5.2	Team around the Children	336

11.5.3	Engagement with the community.....	341
11.6	Impact through the ICF lens	343
11.6.1	Body structure and function-improving endurance	343
11.6.2	Activity and personal factors	346
11.6.3	Participation	349
11.7	Managing expectations	351
11.7.1	Adverse events /side effects.....	351
11.7.2	Variability in response to injections - how long does it last?	353
11.7.3	BoNT-A Re-injection	355
11.8	Measuring Outcome- are we measuring what matters to families?	363
11.8.1	Capacity vs Performance.....	363
11.8.2	Goal setting	366
11.8.3	Quality of life and Participation	368
11.9	Children’s perspective on BoNT-A.....	371
11.9.1	Drivers for Treatment	372
11.9.2	Keeping up with peers	373
11.9.3	The injection procedure and beyond.....	374
11.10	Discussion	378
11.11	Strengths and Limitations.....	382
11.12	Future research	386
Chapter 12	Integration and triangulation of Phase I and Phase II findings.....	387
12.1	Synthesis and implications	390
12.2	Summary.....	396
12.3	Strengths and Limitations.....	398
12.4	What this study adds to clinical practice.....	399
12.5	Recommendations for future research	403

12.6	Conclusion	404
Chapter 13	References.....	405
Chapter 14	Appendices.....	431
14.1	Ethical Approval.....	431
14.2	Patient Information Sheets (PIS) / Assent Forms- Examples	437
14.3	Study Manual.....	452
14.4	QFM Scoring	462
14.5	Interview Schedules	466
14.6	COPM Goals.....	472
14.7	Statistics.....	474
14.7.1	Statistics- Normality Tests.....	474
14.8.1	Statistics -Non Parametric descriptive data and Tests	481
14.8.2	Statistics- Mann Whitney U Tests Missing Data Analyses	485
14.8.3	Statistics- QFM Intra-rater reliability	496
14.8.4	Statistics -QFM Correlation	499
14.8.5	Statistics – Multilevel Regression: The Bayesian Information Criterion 503	
14.9	Systematic Review.....	504
14.9.1	Systematic review -PROSPERO protocol.....	504
14.9.2	Systematic Review-Medline Search	507
14.9.3	Data Extraction Form- instructions for reviewers.....	508
14.9.5	Systematic Review- Levels of evidence and Conduct questions AACPDMD	512
14.9.6	Systematic Review – Table of methodology and results of included studies	513
14.10	Thematic analysis	523
14.11	Publications related to the current study	569

List of Figures

Figure 1-1 Gross Motor Function Classification System (Palisano et al., 1997)	42
Figure 1-2 World Health Organization's International Classification of Functioning, Disability and Health -Children and Youth Model ICF-CY	44
Figure 1-3 Mechanism of Normal Transmitter release (A) and Action of Botulinum Toxin A (B)	46
Figure 1-4 Botulinum toxin type A (BoNT-A) mechanism of action]	47
Figure 2-1 International Classification of Functioning Disability and Health, (ICF)(WHO, 2007)	65
Figure 2-2 PRISMA style flowchart of BoNT-A Studies in Children with CP.....	73
Figure 2-3 Outcome measures used in the included studies within their ICF domains	81
Figure 2-4 Summary of short-term and long-term significant changes in the BSF domain following BoNT-A	93
Figure 2-5 Summary of short-term and long-term significant changes in Activity domain following BoNT-A	97
Figure 2-6 Summary of short-term and long-term significant changes in the Participation domain following BoNT-A.....	102
Figure 4-1 Study Outcome Measures within ICF Domains	130
Figure 4-2 Categorisation of injected lower limb muscle groups: proximal, distal and multilevel.....	132
Figure 4-3 Diagrammatic representation of the Modified Tardieu Scale (MTS)	138
Figure 4-4 Faces Pain Scale	139
Figure 5-1 Study flow chart according to CONSORT guidelines.....	145
Figure 5-2 Age grouping by GMFCS Level	150
Figure 5-3 Number of previous BoNT-A injection episodes	151
Figure 5-4 Muscles injected in the study	154
Figure 5-5 Muscle groups injected within GMFCS Levels	155
Figure 5-6 Treatment session as related to age groups.....	156
Figure 6-1 Mean QFM Attribute Scores across all time points.....	163

Figure 6-2 Scatter plot showing Baseline correlations of QFM attributes highlighting GMFCS levels ($0.88 < r < 0.98$)	165
Figure 6-3 Box Plot of mean % QFM attribute scores at all time points N=48	167
Figure 6-4 QFM Alignment scores by GMFCS Levels (n=48).....	169
Figure 6-5 QFM Alignment scores by reinjection within the study (n=48).....	170
Figure 6-6 QFM Co-ordination Scores by GMFCS Level	171
Figure 6-7 QFM Co-ordination Scores by reinjection within the study.	172
Figure 6-8 QFM Dissociated Movement Scores by GMFCS Levels.	173
Figure 6-9 QFM Dissociated Movement score by re-injection within the study.....	174
Figure 6-10 QFM Stability Scores by GMFCS Levels.....	175
Figure 6-11 QFM Stability Scores by re-injection in the study.	176
Figure 6-12 QFM Weight shift Scores by GMFCS Levels.	177
Figure 6-13 QFM Weight shift Scores by re-injection in the study.....	178
Figure 6-14 Bland Altman Plot representing intra-rater agreement for QFM Alignment scores.....	181
Figure 6-15 Bland Altman Plot representing intra-rater agreement for QFM Alignment scores.....	182
Figure 6-16 Scatter plot matrices showing correlation of QFM attributes at 6 weeks post BoNT-A	183
Figure 6-17 Scatter plot matrices showing correlation of QFM attributes at 6 months post BoNT-A	184
Figure 6-18 COPM Goals set at baseline showing the number of goals within each ICF Domain	187
Figure 6-19 COPM Response Total Individual Goal (orange) vs Average Goal Score (blue)	191
Figure 6-20 Boxplot showing improvement from baseline (T0) in COPM P (performance) scores and COPM S (satisfaction scores).....	194
Figure 6-21 Mean COPM Averaged Performance Scores.....	194
Figure 6-22 Mean COPM Averaged Satisfaction Score.....	195
Figure 6-23 Mean Averaged COPM Performance score by re-injection within the study.....	197

Figure 6-24 Mean Averaged COPM Satisfaction score by re-injection within the study.....	197
Figure 6-25 COPM Performance scores over 12 months by GMFCS Level.....	198
Figure 6-26 COPM Satisfaction scores over 12 months by GMFCS Level.....	199
Figure 6-27 COPM Goal type by ICF Domain and GMFCS Level.	200
Figure 6-28 COPM Performance scores for Individual goals.	201
Figure 6-29 COPM Satisfaction scores for Individual Goals.....	202
Figure 6-30 Individual COPM Performance scores by ICF Domain (n=129)	
Figure 6-31 Individual COPM Satisfaction scores by ICF Domain (n=129)	204
Figure 6-32 Mean COPM-P BSF Goal Score by re-injection within the study.....	205
Figure 6-33 Mean COPM-P A&P Goal Score by re-injection within the study.....	206
Figure 6-34 Mean COPM-Satisfaction BSF Goal Score by re-injection within the study	207
Figure 6-35 Mean COPM-S A&P Goal Score by re-injection within the study.....	207
Figure 6-36 COPM Performance Scores response status by ICF Goals over 12 months post BoNT-A	208
Figure 7-1 Modified Tardieu Scale (MTS) reproduced with permission Boyd (2022)	213
Figure 7-2 Mean change in dynamic catch R1 Gastrocnemius (n=59).	215
Figure 7-3 Mean dynamic catch R1 in Gastrocnemius by re-injection status.	216
Figure 7-4 Mean dynamic catch (R1) in Hamstrings.	217
Figure 7-5 Mean dynamic catch (R1) in Hamstring muscles by re-injection status	218
Figure 7-6 Boxplot showing Median SMC scores over 12 months and 25 th and 75 th centiles (n=70).....	219
Figure 7-7 Mean m FPS Pain scores over 12 months (n=47).	220
Figure 7-8 Technical response over 12 months following BoNT-A injections	226
Figure 7-9 Technical response at T3 comparing single versus re-injection groups.	227
Figure 7-10 Mean TUG score all GMFCS levels across 12 months (n=48).	231
Figure 7-11 Mean TUG scores by GMFCS level.....	232
Figure 7-12 Mean 1MFWT distance walked all GMFCS levels over 12 months n=48.	233
Figure 7-13 Mean 1 MFWT distance walked highlighted by GMFCS level	234

Figure 7-14 Mean GMFM-66 score all GMFCS levels n=48.....	235
Figure 7-15 GMFM-66 scores by GMFCS level across 12 months n=48.	236
Figure 8-1 Study outcome measures within ICF Domains used for multilevel regression analysis * Primary outcome measures.....	243
Figure 10-1 Examples of craft activities for interviews with children.....	304
Figure 10-2 Reflexive Thematic Analysis (Braun and Clarke, 2019).....	306
Figure 11-1 Final Thematic map based on Braun and Clarke (2019)	311
Figure 12-1 Modified ICF adapted from CanChild (Rosenbaum and Gorter, 2012)	394
Figure 12-2 A modified biopsychosocial approach to functioning (adapted from (Kraus de Camargo et al., 2019).....	396

List of Tables

Table 2-1 Inclusion and exclusion criteria for articles included in the systematic review.....	69
Table 2-2 Summary of included studies.....	74
Table 2-3 Demographics of included studies and outcomes used	82
Table 2-4 Conduct Rating Tool (AACPDm).....	86
Table 2-5 Systematic Review Results by ICF Domains showing short-term and long-term statistical significance of outcomes following BoNT-A	105
Table 3-1 Eligibility criteria for The Toxin Study	125
Table 4-1 Timings of study assessments T0-T3.....	129
Table 4-2 Study Outcome Measures throughout ICF	143
Table 5-1 Baseline characteristics of participants	148
Table 5-2 Clinical characteristics of study participants.....	149
Table 5-3 Muscles injected and details of BoNT-A (abobotulinumtoxinA) dose D=Distal muscle groups P=Proximal muscle groups	152
Table 5-4 Number of muscles injected in one injection episode	152
Table 5-5 Combination of muscle groups injected during the study per participant	153
Table 6-1 MDC Scores for QFM.....	162
Table 6-2 Mean QFM percentage scores for the total sample.....	163
Table 6-3 Mean QFM scores by GMFCS level	164
Table 6-4 One way repeated measures ANOVA for QFM attributes (effect of Time)	166
Table 6-5 Mean Change score QFM attributes from baseline scores	167
Table 6-6 QFM Scoring time (minutes)	179
Table 6-7 QFM Intra-rater reliability statistics.....	180
Table 6-8 Pearson correlation for QFM attribute scores at 6 weeks post BoNT-A .	183
Table 6-9 Pearson correlation for QFM attribute scores at 6 months post BoNT-A	184
Table 6-10 Power calculation for QFM attributes	185
Table 6-11 Response to BoNT-A for averaged COPM Performance and Satisfaction scores	190

Table 6-12 Response to BoNT-A for individual COPM Performance and Satisfaction scores	190
Table 6-13 One way repeated measures ANOVA for Averaged COPM scores (effect of Time)	193
Table 6-14 Mean change Averaged COPM Performance Score	195
Table 6-15 Mean change Averaged COPM Satisfaction scores	196
Table 6-16 One way repeated measures ANOVA for Individual COPM scores (effect of Time)	201
Table 6-17 Mean change Individual COPM Performance Score	202
Table 6-18 Mean change Individual COPM Satisfaction scores	203
Table 6-19 Mean Individual COPM Performance Scores by ICF Domain	205
Table 6-20 Mean Individual COPM Performance Scores by ICF Domain	206
Table 7-1 Summary of descriptive statistics for Body Structure and Function (BSF) measures	212
Table 7-2 Mean change in R1 Hamstrings and Gastrocnemius muscles	214
Table 7-3 Definition of Technical Response for bilateral injections	225
Table 7-4 Activity outcome measures	230
Table 7-5 Mean TUG scores (seconds) by GMFCS level	232
Table 7-6 1MFWT Mean distance walked (metres) by GMFCS level	234
Table 7-7 Mean GMFM-66 scores for total sample by GMFCS level	236
Table 7-8 Participation scores descriptive statistics and statistical analysis	240
Table 8-1 Complete multilevel regression model for QFM Alignment	247
Table 8-2 Complete multilevel regression model for QFM Co-ordination	248
Table 8-3 Complete multilevel regression model for QFM Dissociated Movement	249
Table 8-4 Complete multilevel regression model for QFM Stability	250
Table 8-5 Complete multilevel regression model for QFM Weight shift	251
Table 8-6 Complete multilevel regression model for COPM-Performance	253
Table 8-7 Complete multilevel regression model for COPM Satisfaction	254
Table 8-8 Complete multilevel regression model for MTS R1 Gastrocnemius muscle	255
Table 8-9 Complete multilevel regression model for MTS R1 Hamstring muscle ..	256
Table 8-10 Complete multilevel regression model for SMC outcome	258

Table 8-11 Complete multilevel regression model for TUG outcome.....	259
Table 8-12 Complete multilevel regression model for 1MFWT outcome	260
Table 8-13 Complete multilevel regression model for GMFM-66 outcome.....	261
Table 8-14 Complete multilevel regression model for CPQOL Participation outcome	263
Table 8-15 Complete multilevel regression model for CPQOL Function outcome..	263
Table 8-16 Complete multilevel regression model for PEM-CY Home Frequency Participation outcome.....	264
Table 8-17 Complete multilevel regression model for PEM-CY Home Involvement Participation outcome.....	265
Table 8-18 Complete multilevel regression model for PEM-CY School Frequency of Participation outcome.....	266
Table 8-19 Complete multilevel regression model for PEM-CY School Involvement in Participation outcome.....	266
Table 8-20 Complete multilevel regression model for PEM-CY Community Frequency of Participation outcome	267
Table 8-21 Complete multilevel regression model for PEM-CY Community Involvement in Participation outcome	268
Table 8-22 Summary of the results from the Hierarchical Multilevel Regression Models.....	269
Table 10-1 Summary of response to BoNT-A for Phase II.....	301
Table 10-2 Six phase framework of reflexive thematic analysis (Braun and Clarke, 2019)	305
Table 11-1 Demographics for participants in Phase II of the study.....	309
Table 11-2 Themes and sub-themes generated from the data.....	310
Table 12-1 Synthesis of quantitative phase I data with qualitative phase II data X Divergence of Phase II data from Phase I data [*following adjustment for clinical confounders]	389

Chapter 1 Introduction

This report presents the work of a 6-year part-time NIHR Funded Clinical Doctoral Fellowship. This thesis is written from the perspective of the researcher (LK) who has over thirty years' experience of working as a clinical physiotherapist with children and young people with cerebral palsy (CYPwCP).

1.1.1 Introducing the researcher

LK's interest in the use of Botulinum Toxin for the management of increased tone in cerebral palsy stems from extensive experience working with this population as a lead clinical specialist physiotherapist; through setting up one of the largest services for this treatment in the UK and becoming one of the first paediatric non-medical injectors. This long standing clinical academic interest in the use of BoNT-A to manage dynamic tone began in 1993, as part of the UK Botulinum Toxin and Cerebral Palsy Working Party (Carr et al., 1998). LK could see that the novel intervention of BoNT-A was potentially useful in reducing spasticity but was keen to evaluate the efficacy of BoNT-A beyond the muscle level and explored the effects of treatment on improving a child's motor function (MSc dissertation (Katchburian, 1997)).

Since that time BoNT-A has become an internationally accepted treatment modality, with an exponential increase in the use of botulinum toxin in children with cerebral palsy. However, there have been concerns raised that BoNT-A may currently be overprescribed (Multani et al., 2019a) with excessive injection cycles and little evaluation of the benefits. Whilst efficacy in terms of spasticity reduction has been established there is an increased need to evaluate the efficacy of this treatment on other outcomes considered more meaningful to children such as improved activity and participation.

Experience in LK's clinical practice suggested that parents frequently reported changes following BoNT-A in areas such as improved quality of movement, which were not evaluated by any of the standardised outcome measures used in clinical

practice. There were concerns that in the absence of sensitive outcome measures throughout the ICF, and accurate means of evaluating the efficacy of BoNT-A, treatment may not be targeted to the right patient, at the right time, or continued for the right length of time.

1.1.2 Overview and context of the PhD

Cerebral Palsy (CP) is the most common cause of physical disability in childhood (Odding et al., 2006). Although the initial brain insult is described as static, the effects of the neurological involvement are dynamic and change with time and growth of the child (Molenaers et al., 2010). Increased tone (also referred to as hypertonia or spasticity) is considered one of the primary motor impairments in CYPwCP (Koman et al., 1994) and a significant contributor to secondary musculoskeletal impairments (such as ankle, knee and hip contractures) impacting on activity and participation (Koman et al., 2003).

Over the last 20 years intramuscular Botulinum Toxin A (BoNT-A) has become an internationally accepted treatment modality for the management of hypertonia in overactive muscle groups (Ward et al., 2006). Historically most of the evidence has been related to impairment outcomes (restriction of body functions and structures) rather than measures of activity and participation (as defined in the World Health Organisation's Framework (Figure 1-2) *International Classification of Functioning, Disability and Health- children and youth model (ICF-CY)*). In addition, much of this evidence has been based on short term outcome (12-16 weeks or less).

Research suggests that it is essential to assess meaningful outcomes by evaluating adaptive skills (such as activity and participation) and quality of life (QOL) following interventions for CP in order to improve targeted intervention for CYPwCP (Molenaers et al., 2013, Tilton et al., 2017).

There is little evidence demonstrating that BoNT-A treatment has a positive effect on the areas of children's lives which are most meaningful to them (Tilton et al., 2017). Whilst the short-term impact of BoNT-A on impairment has been

investigated, less is known about the longer term impact of treatment over three months or the effect on movement quality, activity and participation. These areas have been identified as a priority of research relevance by the CP community, identified in the top ten research priorities linked to the James Lind Alliance Paediatric Neurodisability research priority setting programme:

“What is the long-term effectiveness of Botulinum neurotoxin A in children and young people with neurodisability?” (Morris et al., 2015)

and within the NICE Spasticity guidelines which stated further research was required to evaluate the effectiveness of BoNT-A;

“Outcomes related to gross motor function and evaluation of participation in activities should be evaluated” (NICE, 2012)

There is an international drive to optimise the use of BoNT-A in CYPwCP by providing timely intervention to the right patient groups for the right length of time (Multani et al., 2019a, NICE, 2012, Strobl et al., 2015).

LK’s experience in an established tertiary referral motor disorder service suggested that lower limb BoNT-A injections could be beneficial for ambulant CYPwCP with accurate patient selection, goal setting and evaluation of response. However, there remained many unanswered questions regarding BoNT-A’s impact on activity, participation and QOL, together with uncertainty about the duration of response and possible adverse effects both in the short and long-term.

1.1.3 Aims and objectives of the PhD

A comprehensive review of the literature was undertaken to determine the existing evidence regarding the use of BoNT-A in CYPwCP (Chapter 1.2). This suggested a lack of information evaluating the benefits of BoNT-A treatment on activity, participation and quality of life. This was then followed by a systematic review of the existing literature to determine the benefits of BoNT-A treatment when evaluated through all domains of the ICF (Chapter 2). This highlighted a paucity of

high quality studies investigating change in all of the ICF domains following lower limb BoNT-A.

The subsequent research programme developed within the PhD aimed to contribute to this evidence base. It did this by investigating the multidimensional response to BoNT-A treatment in ambulant CYPwCP within all domains of the ICF over a 12 month period using standardised outcome measures in an established tertiary level service. Through identifying response patterns to BoNT-A in key aspects of health across all domains of the ICF and by not restricting outcome to change at impairment level, this study aimed to provide clinicians and families with more meaningful information to inform future treatment planning and optimise the use of BoNT-A in CYPwCP

This evidence was further supplemented by the introduction of a novel validated outcome tool the Quality Function Measure (QFM), not previously reported in the literature following BoNT-A use in CP. The QFM evaluated change in movement quality, considered an essential component of effective gross motor skills in children with CP, following the use of BoNT-A.

1.1.4 Research Questions

Specifically the aims of this research were:

1. To investigate clinical and patient reported outcomes throughout the ICF domains (body structures and function, quality of movement, activities and participation and quality of life) at 6 weeks, 6 months and 12 months following lower limb BoNT-A injections in ambulatory CYPwCP.
2. Determine the factors (including GMFCS level, age, injection history) associated with a response to BoNT-A treatment over a 12-month period
3. Explore families' experience of BoNT-A treatment and investigate how standardised clinical outcome measures relate to child and parent perceptions of response following BoNT-A treatment.

Evidence was generated as to the responsiveness of standardised outcome measures in relation to change post BoNT-A, as well as the relationship between standardised outcome measures used to capture treatment effect and children's and families' perception of outcome. Change was analysed following adjustment for clinical confounders and was related to established clinically significant parameters.

1.1.5 Patient and public involvement and engagement (PPIE)

CYPwCP and their parents were involved in the development of this research, exploring the importance of the research, the appropriateness of the research questions, the acceptability of the research methods and best methods for disseminating findings. Fifteen ambulant CYPwCP receiving BoNT-A at GOSH and their parents were consulted. A wider population of CYPwCP and their parents were also consulted via the SCOPE website, the advisory group for CYPwCP at Brunel University and Young People's Advisory Group (YPAG) at GOSH.

Reference Group/ Steering Group

Three parents (all mothers) and three CYP (two boys and one girl -not participants) agreed to continue advising on the study through membership of the study steering group (parents) or reference group (CYP). Three professionals (two physiotherapists and one doctor) also formed part of the steering group. By including children and families perspectives together with regular contributions from practicing clinicians within the service we guaranteed the inclusion of important values and preferences from families and clinicians alike. This ensured that the findings of the study remained relevant and applicable to the management of CYPwCP (INVOLVE, 2016, Nguyen et al., 2018, Wright et al., 2008)

1.1.6 Thesis outline

This thesis consists of twelve chapters and is divided into three sections:

- *A Systematic review of the existing research evaluating BoNT-A efficacy within all ICF domains.*
- *Phase I Quantitative study exploring the effects of lower limb BoNT-A use over a 12 month period with outcomes reflecting all domains of the ICF*
- *Phase II Qualitative study exploring children and families' experience of BoNT-A use.*

Structure

This PhD thesis takes the following structure:

- **Chapter 1** provides a background to the study undertaken with a summary of the current literature regarding the use of lower limb BoNT-A use in ambulant CYPwCP.
- **Chapter 2** is a systematic review of the literature regarding the efficacy of BoNT-A as measured using all domains of the ICF
- **Chapter 3** defines the aims and objectives of Phase I and II of the Research programme and the development of the research programme
- **Chapter 4** details the methodology for the Phase I Quantitative study
- **Chapter 5** presents the demographics of the sample population including clinical data regarding children's treatment in Phase I of the research
- **Chapter 6** summarises the results of univariate analysis of Phase I Primary outcomes- Change in movement quality as measured by the QFM and goal attainment as measured by the Canadian Occupational Performance Measure (COPM)
- **Chapter 7** summarises the results of univariate analysis of Phase I Secondary outcomes- measured throughout the ICF domains of body structure and function, activity and participation.

- **Chapter 8** summarises the results of multivariate analysis of Phase I primary and secondary outcomes following the adjustment for clinical confounders using hierarchical multilevel modelling.
- **Chapter 9** presents the discussion and conclusions of the Phase I study
- **Chapter 10** details the research methodology for the Phase II Qualitative study and presents a summary of the sample population demographics for Phase II.
- **Chapter 11** presents the results of the thematic analysis of the Phase II qualitative data.
- **Chapter 12** presents the integration of Phase I and Phase II findings with recommendations for future research and concluding comments.

1.2 Background

In order to provide context to the study this chapter presents a brief summary of the existing literature by considering;

- The clinical presentation and classification of Cerebral Palsy- including the World Health Organization's International Classification of Functioning, Disability and Health -Children and Youth Model (ICF-CY)
- Current evidence for BoNT-A injections in the management of lower limb muscle hypertonia in ambulant CYPwCP. This will include; mechanism of action, age at injection and re-injection intervals, side-effect profile and adverse events including evidence of histological changes in CP muscle following BoNT-A use.

Whilst it is recognised that BoNT-A is used for other indications in CYPwCP, this study limits its focus to the use of BoNT-A in lower limb muscles of ambulant CYPwCP. The aim of the rest of this chapter is to explore the existing knowledge on the use of lower limb BoNT-A in the management of ambulant CYPwCP and investigate how efficacy has been assessed to date in order to identify any gaps in the current literature.

1.3 Cerebral Palsy

Cerebral palsy (CP) describes *“a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain”*(Bax et al., 2005). The motor disorders of CP are often accompanied by “disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and secondary musculoskeletal problems “(Sanger et al., 2003). CP is the most common physical neurodisability of childhood and is the greatest cause of referral to rehabilitation services of all paediatric diagnoses (Odding et al., 2006). It has a life-long impact on children and young people (CYP) and families, with a prevalence of 2-3 per 1000 live births throughout Europe and 110,000 affected individuals in the UK (Cans et al., 2002, Sawyer et al., 2011). Although the initial cerebral insult is static, the effects of the neurological involvement are dynamic and the clinical manifestations of CP change over time as children grow and develop. (1.3.1). Interventions should be considered carefully, taking into account current difficulties, functional goals, family preferences and also the likely prognosis.

1.3.1 Classification of Cerebral Palsy

Several classification systems are used to categorise children and young people with CP (CYPwCP) into different subgroups

These classifications are based primarily on;

- The dominant abnormality of muscle tone (hypertonia or hypotonia)
- The diagnosed movement disorders such as spastic, dyskinetic or ataxic
- The anatomical distribution such as unilateral or bilateral involvement

The majority of CYPwCP (over 80%) experience hypertonia. There are different types of hypertonia described in the literature, including spasticity, rigidity and hypertonia of dystonia. (SCPE, 2002) (Cans et al., 2002).The picture is often mixed and can be characterised by stiff or tight muscles, with components of spasticity- an

involuntary, velocity dependent increase in tonic stretch reflex with exaggerated tendon jerks (Lance, 1980) and dystonia-characterised by increased muscle spasm associated with abnormal postures (Nguyen et al., 2018, Sanger et al., 2003).

Hypertonia is considered one of the primary motor impairments in CYPwCP. One of the main features is the presence of increased dynamic muscle tone, which limits muscle movement around a joint, interferes with voluntary selective motor control and often results in secondary impairments such as pain, joint contracture and bony deformities. The progression of dynamic contracture to fixed contracture is a fundamental issue in the care of CYPwCP. Adaptive changes in the muscle and impaired muscle growth affect bone growth and can result in further movement limitation (Koman et al., 1993).

In CYPwCP, abnormalities in skeletal muscle include reduced muscle-belly length, muscle volume, and cross-sectional area in comparison to typically developing muscles (Barrett and Lichtwark, 2010). Damiano et al. (2001) also described decreased muscle thickness and volume, decreased moment-generating capacity and weakness. Key findings in contracture development in CYPwCP appear to include changes at both the macroscopic and microscopic levels in terms of structure and muscle biomechanics; including change in sarcomere length, fibre type, bundle stiffness, extracellular-matrix (ECM) concentration, and stem-cell numbers (Mathewson and Lieber, 2015). It is thought that the reasons for muscle weakness in CYPwCP can be categorized into 3 main areas: loss of muscle mass, reduced contractile material with more connective tissue and fat, and overstretched sarcomeres (Verschuren et al., 2018).

These secondary motor impairments of CP commonly interfere with functional mobility, positioning, and self-care which has a major impact on daily personal activities that can restrict participation both in school and community environments (Preston et al., 2011).

This can also influence function in adult life as CYPwCP often reach adolescence with substantial impairments in the volume and functional capacity of significant

muscles, and are therefore at greater risk of developing age-related sarcopenia (a loss of function associated with a loss of muscle mass (Cao and Morley, 2016)) than typically developing adults, and as a consequence may have a loss of functional capacity at an earlier age (Graham et al., 2016, Shortland, 2009)

1.3.2 The Gross Motor Function Classification System (GMFCS)

Children with CP can be further classified dependent on their functional gross motor abilities. The Gross Motor Function Classification System (GMFCS) is a validated 5-level ordinal scale that describes and classifies the severity of gross motor involvement and resultant movement ability of CYPwCP of both unilateral and bilateral distribution (Palisano et al., 1997). It classifies children into one of five levels, where level I describes the most able ambulant children and Level V the most severely affected children with no independent mobility (Figure 1-1).

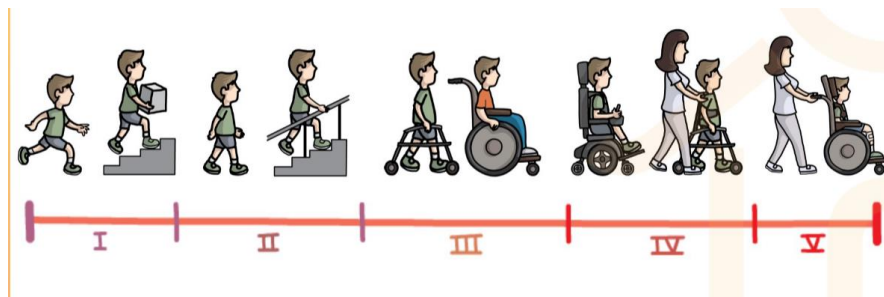


Figure 1-1 Gross Motor Function Classification System (Palisano et al., 1997)

The GMFCS has been pivotal in CP management since its introduction in 1997 and has been shown to be a valid and reliable scale (Wood and Rosenbaum, 2000). It provides families, clinicians and researchers with a common language, facilitating discussion of a child's current and predicted motor ability. The GMFCS has improved the comparison of CYPwCP within individual GMFCS levels in what remains a very heterogeneous population (Palisano, 2006). There is now an accepted use of the GMFCS in interventional studies involving children with CP and increasingly populations are divided into ambulant CYPwCP (GMFCS I-III) and non ambulant CYPwCP (GMFCS IV-V) for research studies (Mandaleson et al., 2014).

Motor development curves have been produced for each GMFCS level (Palisano et al., 1997). These describe change in gross motor function over time and provide clinicians with evidence of the natural history of CP thereby allowing the opportunity to discuss prognosis and interventions more effectively with families (Rosenbaum et al., 2002). Recent evidence suggests that motor function in GMFCS levels may not be stable into adolescence and a deterioration in gross motor function may be observed (Hanna et al., 2009). Clinicians are aware of this potential deterioration in function as a child matures. Interventions to reduce hypertonia are frequently used to supplement ongoing physical therapy in an attempt to limit or delay this reduction in function and its resultant impact on activity and participation. These include systemic medication, focal reversible interventions such as BoNT-A, together with more permanent interventions for tone management such as Selective Dorsal Rhizotomy and orthopaedic surgery.

1.3.3 The World Health Organization's International Classification of Functioning, Disability and Health -Children and Youth Model ICF-CY

The World Health Organization's International Classification of Functioning, Disability and Health -Children and Youth Model **ICF-CY** (WHO, 2007) forms the conceptual foundation for what is now the most widely adopted global framework for the definition and measurement of health and disability. In combination with the GMFCS, the ICF provides a standard language for international and multidisciplinary use and is commonly used to discuss assessment, goal setting and evaluation of interventions in health conditions such as CP (Figure 1-2). Evaluation of each dimension of the ICF for an individual provides a representation of a child's experience of living with a disability.

Within the field of neurodisability, there is a move away from focusing predominantly on impairment at body structures and function level (e.g. brain injury, spasticity, weakness), towards an increased recognition of the importance of goals relating to limitations in activity and restrictions in participation (Nguyen et al., 2016). Quality of life (QOL), whilst not officially referred to in the ICF framework

is also increasingly being used as an endpoint in clinical outcomes research and is ideally assessed through both carer and child self-report report (Gordon, 2014).

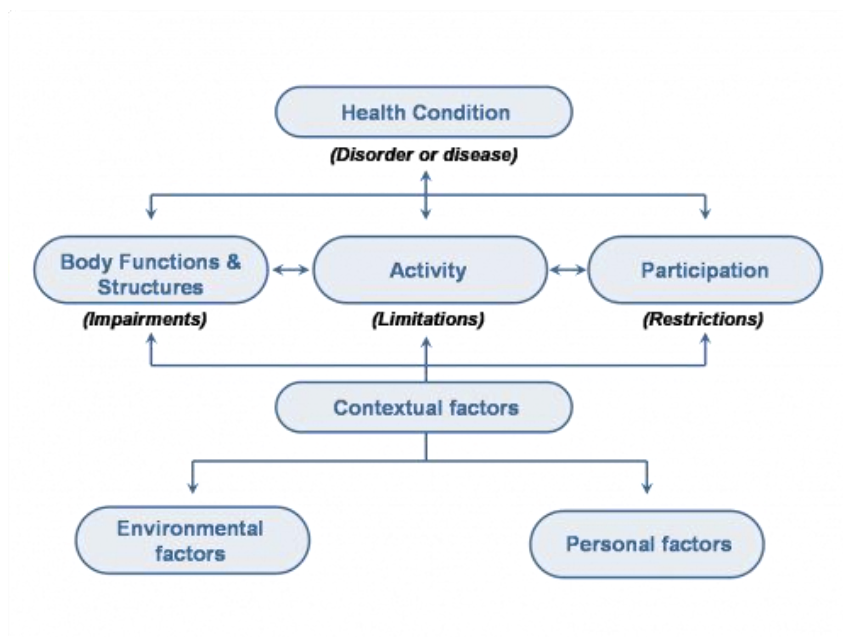


Figure 1-2 World Health Organization's International Classification of Functioning, Disability and Health - Children and Youth Model ICF-CY

Reviews of paediatric outcome measures have recommended evaluation of daily life activities, adaptive skills (i.e. activities and participation), and QOL if clinicians are to assess realistic outcome and target interventions that are meaningful to children and families (Jette and Haley, 2005, Msall et al., 2003, Novak et al., 2013).

The use of outcome measures throughout all domains of ICF (including environmental factors and personal motivation) can be used to inform clinical thinking, practice and research in the field of CP. The ICF provides a system for classifying the focus of outcome studies and can help to identify gaps in current knowledge (Gordon, 2014). Evaluation of outcomes throughout the ICF is particularly pertinent when considering the effects of interventions for tone management such as BoNT-A on CYPwCP. Each dimension of the ICF provides a representation of living with a disability for a CYPwCP.

Although BoNT-A treatment specifically targets impairment at a body structure and function level, evaluation of impairment without taking into account the changes in activity and participation, restricts understanding of the effect of the intervention on a child's daily life. There has been little investigation into the degree to which change in impairments of body structures correlate with a change in activity and participation (Rosenbaum, 2003, Rosenbaum, 2020, Strobl et al., 2015, Wright et al., 2008). However, the goals of the intervention are broader than changes at impairment level and should be directed at enhancing functional capacity and improving a child's QOL (Damiano et al., 2021, Rosenbaum, 2021a). As the recent systematic review from the WHO Rehabilitation Programme and Cochrane Rehabilitation group has highlighted, there is increasing pressure on clinicians and researchers to evaluate the outcome of interventions for CYPwCP stating

“if an intervention fails to enhance the quality of life, activity or participation for that child or family either in the short or long term, is it justifiable?” (Damiano et al., 2021)

Therefore to realistically assess meaningful benefit to children and families outcome should be evaluated in all ICF areas.

1.4 Botulinum Neurotoxin -Type A (BoNT-A)

1.4.1 BoNT-A- mechanism of action

Botulinum Neurotoxin (BoNT) is one of the most toxic substances known to man (Lamanna, 1959). Produced by the anaerobic bacterium *Clostridium Botulinum*, it consists of seven different serotypes A to G. Botulinum Neurotoxin Type A (BoNT-A) is the most commonly used in the paediatric clinical setting (Aoki and Guyer, 2001, Papavasiliou et al., 2013, Rasetti-Escargueil et al., 2018).

BoNT consists of an N-terminal light chain (LC, 50 kDa), which is a metalloprotease, connected to a C-terminal heavy chain (HC, 100 kDa) (Albanese, 2011). The heavy chain consists of two principal domains, the N terminal portion, which is the translocation domain that is involved in the release of the light chain into the

cytosol of the motor neuron, and the C-terminal part that is the receptor binding domain, critical for the binding and endocytosis of BoNT-A into the presynaptic neuron(Albanese, 2011).

BoNT-A is injected into skeletal muscle (Figure 1-3 (1)) and produces a reversible local muscle weakness (*flaccid paralysis*); selectively binding with acetylcholine vesicles in the motor nerve to block the release of the neurotransmitter acetylcholine (ACh) at the pre-synaptic cholinergic nerve terminal. This prevents muscle contraction at the neuromuscular junction, resulting in partial paralysis of the injected muscle (Figure 1-3 (2)).

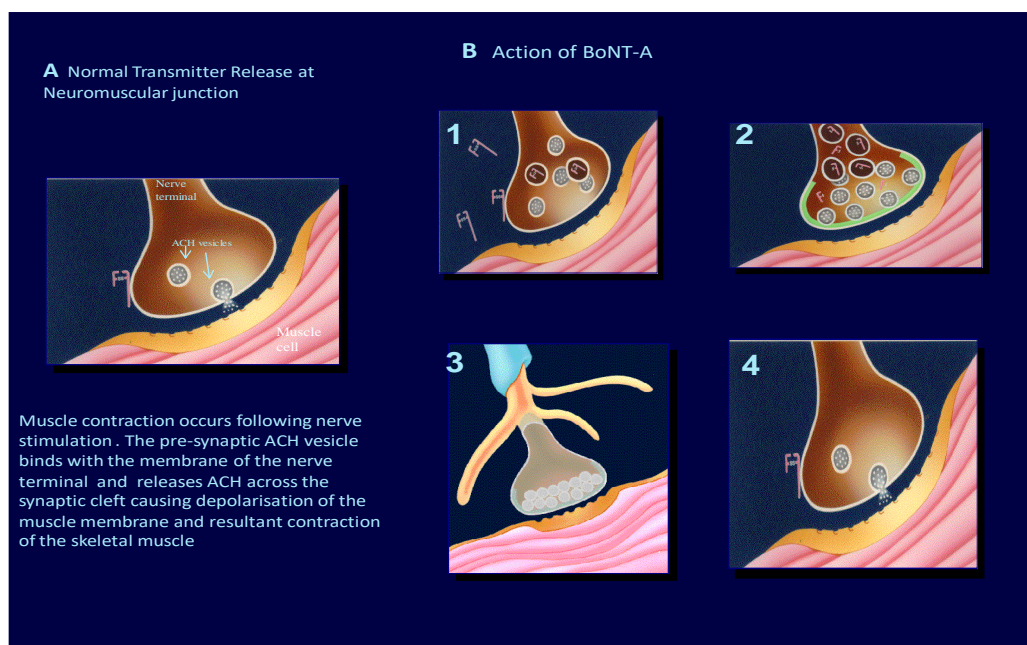


Figure 1-3 Mechanism of Normal Transmitter release (A) and Action of Botulinum Toxin A (B)

The regulation of fusion of the synaptic vesicle with the plasma membrane involves a complex of proteins collectively referred to as SNAREs (Soluble-N Ethylmaleimide, Sensitive Factor Attachment Protein Receptor) or SNAP receptors. The principal SNARE proteins include VAMP/synaptobrevin, the pre-synaptic plasma membrane protein, syntaxin, and the synaptosomal protein, SNAP25. BoNT-A interferes with normal vesicle-membrane fusion by a multi-step process, illustrated in Figure 1-4. The overall effect can be described as a neuro-paralysis or chemical denervation of muscle.

BoNT-A does not cross the blood–brain barrier and although retrograde transfer to the Central Nervous System (CNS) from peripheral injection sites is thought to occur to a limited degree, there is little evidence for direct central effects (Jankovic, 2017). One explanation for central effects is that peripheral chemo-denervation may lead to central reorganisation as a result of neuroplasticity (Park et al., 2002).

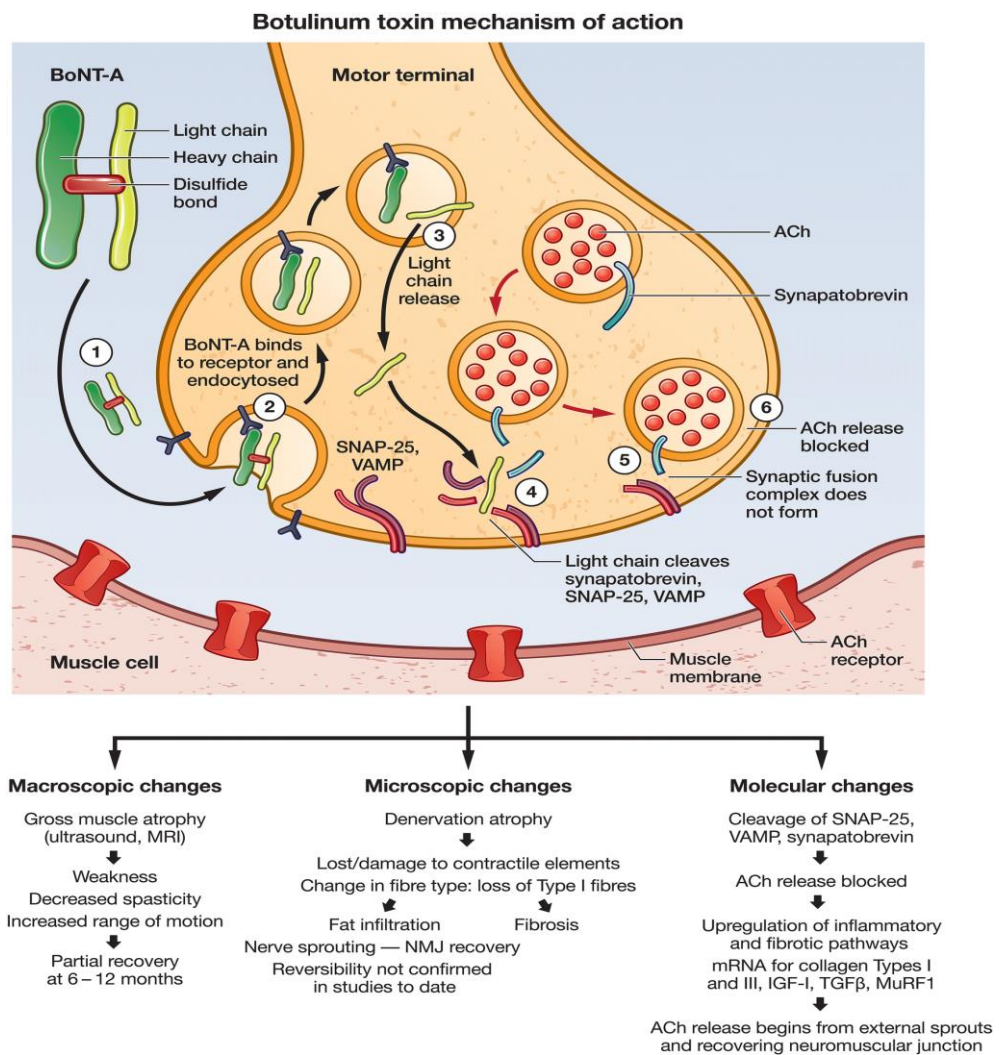


Figure 1-4 Botulinum toxin type A (BoNT-A) mechanism of action

[Reused from (Multani et al., 2019a) for non-commercial /educational purposes under a Creative Commons license

The BoNT-A heavy chain is shown in green and the light chain in yellow, linked by a disulfide bond. Acetylcholine (ACh), the neurotransmitter that is blocked by BoNT-A, is shown as red dots within a circular vesicle in the nerve terminal. The effects of chemo denervation via injection of BoNT-A are summarized at macroscopic, microscopic and molecular levels. SNAP 25, soluble N-ethylmaleimide fusion protein/attachment protein; VAMP, vesicle-associated membrane protein.

]

Whilst the effects can be observed within 24-72 hours following injection, the period of clinically useful relaxation is usually 12 to 16 weeks (Aoki et al., 2006). This period relates to the pharmacological effects of BoNT-A when blockade of acetylcholine release by botulinum neurotoxin type A at the neuromuscular junction induces the formation of an extensive network of nerve-terminal sprouts and the time required for new synaptic connections to occur with collateral sprouting shown in Figure 1-3(3).

An eventual re-establishment of the original neuromuscular junction occurs and return of synaptic activity once the pharmacological effect is complete. An eventual cessation of the sprout outgrowth ensues and, on the eventual return of exoendocytosis to the original terminals, the sprouts gradually lose their ability to perform endocytosis and shortly after start to regress (de Paiva et al., 1999). (Figure 1-3 (4)) (Albavera-Hernandez et al., 2009, Ryll et al., 2011b).

The pattern of sprouting elicited after BoNT-A induced blockade of ACh release is not a precise imitation of the neuronal remodelling seen after other types of injury in the peripheral and central nervous systems. For example, when a peripheral nerve is crushed, motor axons and endplates distal to the injury degenerate and the muscles become denervated (Marder et al., 1997). However, this is in contrast to BoNT-A poisoned terminals, which persist despite their loss of activity.

Nevertheless, an important similarity does exist as both collateral and terminal sprouts are also formed after nerve crush. This results in polyneuronal innervation until these surplus synapses are eventually eliminated. The functionality of terminal sprouts and the overlap in plastic reactions after both nerve injury and BoNT-A poisoning highlight the importance of synaptic remodelling in instigating the eventual recovery of neurotransmission after paralysis. The muscle activity is initially evoked solely via the sprouts in the absence of any exoendocytotic activity within the parent poisoned terminals. It is thought that this may in turn induce a

late phase of the remodelling process culminating in the complete functional repair of the original terminals.

Little evidence exists regarding the timing of recovery of motor axons following BoNT-A specifically in cerebral palsy (Frascarelli et al., 2011, Park et al., 2002) with most work done in the animal model (de Paiva et al., 1999, Jensen et al., 2020, Matak and Lacković, 2015) and adult populations (Chandra et al., 2020). It appears that axon recovery follows a similar trajectory to that in the adult population.

Use of BoNT-A to block Ach release into the synaptic cleft (as shown in Figure 1-4) results in the well-established effect of muscle paresis, often explained as “3 days to take effect, 4 weeks to maximum effect and 3–6 months duration.”(Frascarelli et al., 2011). The clinical effect of BoNT-A appears to continue beyond the point of inducing weakness. Scientific reports are used to discuss the hypothesis that in addition to its effect as local muscle relaxant, BoNT-A acts at the level of the central nervous system (CNS) for ‘reorganization’. It is thought that such an effect on CNS activity could be mediated through afferent pathways coming from the injected site possibly originated in muscle spindles. Its effect through afferent pathways on the CNS may be considered as affording a more long-term response due to this sensory involvement (Giladi, 1997, Hok et al., 2021).

1.4.2 Clinical use of intra-muscular Botulinum Toxin A (BoNT-A)

BoNT-A was first introduced into clinical practice in the 1980’s for the treatment of blepharospasm in the adult population (Scott et al., 1985). However, it was not until 1993, that results of the first clinical trials for the use of BoNT-A to treat lower limb spasticity in CP patients were reported (Koman et al., 1993). The rationale for BoNT-A use in this group was to reduce hypertonia and enhance motor ability and functional skills whilst preventing contracture formation. This represented a major advance in the management of CP (Delgado et al., 2016b). Since this time BoNT-A injections have become an international standard treatment in the management of paediatric hypertonia in CP (Ward et al., 2006). It is often considered a first-line treatment for focal spasticity involving overactive muscle groups, with its’ ability to

reduce spasticity well documented (Alhusaini et al., 2011, Heinen et al., 2021, Hoare et al., 2010, Lukban et al., 2009, Multani et al., 2019a, Tedroff et al., 2009).

Although initial use of BoNT-A was limited to injecting one muscle at a time, it became apparent that many of the common gait abnormalities in CP could only be adequately treated if several muscle groups were treated simultaneously (Friedman and Goldman, 2011).

The progression of dynamic contracture¹ to a fixed contracture in a joint, secondary to spastic muscles, is a fundamental problem in the care of the child with CP (Koman et al., 1993). Targeted BoNT-A treatment temporarily reduces spasticity and muscle hypertonia, resulting in an improved range of motion (Nguyen et al., 2018). During this time of decreased spasticity there is a substantial ‘therapeutic window’ for interventions to address specific pre-determined goals of rehabilitation to optimise functional performance and participation (Thomas et al., 2016). These goals can include targeted motor training, strengthening programmes, stretching (+/- serial casting), splint modification, improved postural management and pain relief (Multani et al., 2019a). Despite the temporary chemical effect within the muscle (approximately 12 weeks), gains in motor function have been reported to persist for longer time periods. There is evidence in the literature of improved motor function observed six months and in some cases over 12 months post injections, particularly when combined with therapeutic adjunctive measures (Bjornson et al., 2007, Dursun et al., 2019, Löwing et al., 2017, Molenaers et al., 2010).

1.4.3 Effectiveness of BoNT-A in CP management

BoNT-A use is well established for the management of hypertonia in both upper and lower limb muscles throughout the GMFCS levels in CYPwCP (Carr, 2009, Delgado et al., 2016b, Desloovere et al., 2001, Gough, 2009, Heinen et al., 2021, Svehlik et al., 2012). International clinical guidelines recommend the use of BoNT-A as an effective (and in most cases) well tolerated treatment for localised spasticity and

¹ Dynamic contracture in a limb has been defined as one that can be corrected to a neutral position with a maximal or submaximal force

muscle hypertonia in this patient group (Delgado et al., 2010, Heinen et al., 2010, Love et al., 2010b, Strobl et al., 2015, Tilton et al., 2017). Within the UK, BoNT-A has been adopted within the evidence-based paediatric National Institute of Clinical Excellence clinical guidelines for spasticity management (NICE, 2012).

Since its introduction over two decades ago, numerous single studies have assessed the effectiveness of BoNT-A on motor function in ambulant CYPwCP, demonstrating an improvement in gait parameters, pain reduction and improved splint tolerance (Boyd and Graham, 1999, Cosgrove et al., 1994, Fehlings et al., 2010, Koman et al., 1993, Nieuwenhuys et al., 2016). Improvements in functional goals over and above those in a non-BoNT-A treatment group have been demonstrated when combined with other rehabilitation treatments (Bjornson et al., 2007). There is also some evidence to suggest that BoNT-A may delay or reduce the need for orthopaedic surgery (Delgado et al., 2016b, Firth et al., 2013, Graham et al., 2008, Graham et al., 2016, Molenaers et al., 2010, Multani et al., 2019a, Tilton et al., 2017).

It is increasingly recognised that successful outcome following BoNT-A treatment is dependent on the integration of targeted injections to appropriately selected spastic muscles and a comprehensive multifaceted rehabilitation programme directed by patient focused goal setting (Desloovere et al., 2007, Franki et al., 2020, Multani et al., 2019a). Whilst a number of single studies have found statistically significant beneficial effects, others have failed to demonstrate significant benefits following BoNT-A (Read et al., 2017, Schasfoort et al., 2018, Sung et al., 2013). The follow up time for assessment varies widely between studies with short term outcome reported as early as 2 to 4 weeks post injection (Delgado et al., 2016b, Dursun et al., 2002, Thompson et al., 1998). The wide variety of assessment tools used may also account for the variability in the reported results, together with a lack of standardisation and little reference to minimum clinically important differences (MCIDs). Both make it difficult to evaluate the clinical benefit of results in the majority of studies. The variety of clinical approaches, adjunctive co-intervention measures and mixed GMFCS levels also contribute to the challenge in interpreting the results of currently available literature regarding the efficacy of

BoNT-A treatment (Friedman and Goldman, 2011, Multani et al., 2019a, Oeffinger et al., 2008).

To date there have been a number of systematic reviews to evaluate the efficacy of BoNT-A use in CYPwCP. In the first Cochrane review of lower limb BoNT-A use, Adesh-Hall and Moore (2000), reviewed the results of three randomized controlled clinical trials (RCTs) for the treatment of lower limb spasticity but failed to find strong evidence “to support or refute” its use in CP. Boyd and Hays (2001), summarised the results of 10 RCTs and found evidence for a moderate, dose-dependent, treatment effect in favour of BoNT-A on gait and lower limb function. Their findings were in keeping with a later meta-analysis of six double-blind RCTs by Cardoso et al. (2006) which demonstrated greater effectiveness of BoNT-A over placebo on the improvement of gait in patients with spastic equinus but this was not evaluated in relation to other domains of the ICF.

Ryll et al. (2011a) later demonstrated mixed results when they systematically reviewed 8 RCTs to assess the efficacy of BoNT-A use on gait. When compared to physiotherapy alone, BoNT-A treatment had a ‘moderate’ positive effect after 2 to 24 weeks of follow up. However this effect was no longer significant when BoNT-A treatment was compared to casting alone. Similarly, Koog and Min (2010) also reported mixed results when they reviewed 15 RCT’s to determine BoNT-A efficacy; observing that when compared to a ‘non- sham’ control, BoNT-A was effective in improving muscle tone, ankle range of motion, gross motor function and gait speed. However when a ‘sham’ injection was used as a control, the results were less favourable and the treatment group demonstrated significant improvement in gross motor function only after 4 months post-treatment. This led the authors to suggest that BoNT-A treatment for ambulant CYPwCP may not be as effective as commonly believed and concerns were raised that it may be over prescribed for this population.

In a later systematic review of interventions for the management of tone in children with CP, lower limb BoNT-A use was found to be effective for reducing

spasticity with the quality of evidence rated as 'high' using the GRADE system (Novak et al., 2013). However, this was in stark contrast to the results of the most recent Cochrane Collaboration report by Blumetti et al. (2019) which reviewed 31 studies with 1508 participants. They concluded that in the context of low quality evidence there was only limited evidence to show that BoNT-A improves walking, joint motion, satisfaction with outcome of treatment or muscle spasticity in CYPwCP in comparison to placebo or usual care.

1.4.4 Optimal age for treatment

Whilst the long-term use of BoNT-A treatment is well established through years of clinical use, many research studies are based on short term outcomes (three months or less) following injection. The evidence base has primarily been based on studies of a single injection episodes but in usual clinical practice-repeat injections are required to realise more long term effects (Delgado et al., 2016b).

Early research using a hereditary spastic mouse model showed that contracture development was completely eliminated in comparison to the control group following a single BoNT-A injection (Cosgrove et al., 1994). This was encouraging to early researchers who postulated that BoNT-A use could potentially eliminate contracture development in the CP population. However, this data could not be fully extrapolated to the human model as the effect of BoNT-A lasted for the entire mouse growth period. This obviously differs in humans where the growth period is far longer than the 3 month pharmacological effect of BoNT-A. Researchers have therefore suggested that whilst contracture development may not be entirely eliminated, its progress may be slowed by repeated BoNT-A use to reduce spasticity (Molenaers et al., 2010, Ryll et al., 2011a, Tedroff et al., 2009).

Within the United Kingdom BoNT-A has a very specific lower limb license for use in *"Calf muscle injections in CYPwCP two years or older within a specialist centre"*. However, in reality, most BoNT-A treatment is 'off- license' use and other age groups and muscles are frequently injected, depending on the clinical indication.

Spasticity commonly develops within the first few years of life in children with CP. However there is a lack of consensus within the literature regarding the optimal age range for BoNT-A treatment, with varying evidence regarding what age treatment should begin and how long treatment should continue (Hastings-Ison et al., 2016). Some authors argue that BoNT-A treatment should only take place between two and six years of age, when the development of motor function is still flexible (Hastings-Ison et al., 2018, Love et al., 2010a, Molenaers et al., 2001, Read et al., 2017). This was supported by a recent systematic review by Eliege de Souza et al. (2014), who investigated the effect of BoNT-A on spasticity and function in six RCTs. They found moderate evidence to support earlier injection in the ambulant population (GMFCS I-III). The authors proposed that first injection before the age of six may result in an 'impairment modifying effect' whilst the gait pattern and motor function are modifiable and before the development of fixed deformity. Others have argued that regular BoNT-A use over a longer period has resulted in delayed and reduced frequency of surgical procedures, with an improved gait pattern when children were assessed at 10 years of age (Desloovere et al., 2007, Franki et al., 2020).

There has been increasing recognition of the different rates of BoNT-A use between older and younger children in a number of international cohort studies. Roquet et al. (2016), looked at BoNT-A use as part of a French national study exploring healthcare in CP. They found BoNT-A was used in 39% of 2-5 year olds and 32% of 12 -17 year old ambulant CYPwCP. Valentine et al. (2021), reported similar rates of use in children under 10 in their Western Australian study. However the rates of use in a Swedish cohort study, although similar in younger children (32% of 4-6 year olds), were significantly lower in the older age group, with 22% of 10-12 year olds and 18% of 13-15 year olds (Franzen et al., 2017).

Whilst age is considered an important factor during patient selection by some researchers, others have suggested it is the degree of dynamic spasticity present pre-injection and GMFCS level which may be of more importance in predicting benefits of treatment (Nguyen et al., 2016). A cut off point for an upper age limit for

treatment has been disputed and a number of researchers have highlighted the benefits of BoNT-A use in the older child, particularly in conjunction with focused goal setting when dynamic spasticity is present, for pain and spasm reduction, postural management and splint tolerance (Autti-Ramo et al., 1997, Strobl et al., 2015, Wissel et al., 1999). However, evidence relating to long term outcome of BoNT-A treatment is lacking with little evidence about repeated injection effects in older children.

Increasingly, studies are beginning to explore BoNT-A use in a younger population of children with CP, in some cases as young as 9 months of age (Bakheit, 2010, Hastings-Ison et al., 2014, Zhu et al., 2016). Zhu and co-workers (2016) carried out an RCT with 80 BoNT-A naïve children (9-36 months) and reported a statistically significant improvement in spasticity scores at six months as measured by Modified Tardieu Scale in children in the BoNT-A plus intensive therapy versus the intensive therapy control group.

1.4.5 Re-injection interval

There is a generally accepted minimum re-injection interval of three months due to the danger of antibody formation, overdosing and increased risk of adverse events² (Baker et al., 2002). However, despite repeated injections being indicated as part of usual clinical practice, there remains little consensus within the literature regarding the time interval for repeat injections. Until recently relatively few studies evaluated repeat injections in children with CP and those available have involved relatively small numbers in what remains a heterogeneous population. In a recent systematic review of nine studies, Kahraman et al. (2016), evaluated the effectiveness of repeated lower limb BoNT-A injections in CYPwCP and identified that the intervals between repeat injections varied between 3 and 12 months; with the injection being repeated a minimum of one and a maximum of 13 times in the participants studied. Whilst they found that CYPwCP showed functional improvements following the first two injection sessions they concluded that there

² Flu like symptoms, generalised weakness, bladder instability, dysphagia (O'Flaherty et al., 2011)

was insufficient evidence to assess the effects of multiple injections over a longer time period. They suggested that variable results following repeated longer term injections may suggest a declining effect with repeated BoNT-A.

Short term results of repeat injection sessions over twelve months in the ambulant child have been shown to demonstrate improvement in gait with a good safety profile and few adverse events² (Delgado et al., 2016a, O'Flaherty et al., 2011). However, longer term studies examining the effect of repeated BoNT-A treatment in ambulant children with CP (GMFCS I-III) have reported more mixed results in gait improvement. In a 24-month study, led by Metaxiotis et al. (2002), 21 children with bilateral CP (naïve to previous BoNT-A), showed improvement in gait parameters following the first two injections, with a reduction in gait improvement reported after third and fourth injections. However, small participant numbers at third (n=6) and fourth (n=3) injection sessions limits the strength of their findings.

Read et al. (2016) investigated the effects of repeated injections in 17 children with bilateral CP (GMFCS I-II) over 3 treatment cycles (7.7 months (s.d.2.2) apart) and suggested that although the first injection of BoNT-A had the greatest impact on gait quality (as measured by the Edinburgh Visual Gait Scale), subsequent injections maintained gait quality, leading the authors to suggest that repeated BoNT-A use may prevent motor deterioration in adolescence.

A recent RCT compared two injection frequency regimens; 12-monthly versus 4-monthly for spastic equinus with 42 BoNT-A naïve ambulant children and found no significant difference in range of ankle motion or secondary outcome measures, (together with less adverse events per child per year) in the less frequent injection group. They therefore suggested less frequent injections were just as efficacious and potentially more cost effective (Hastings-Ison et al., 2016). These results were in keeping with an earlier multicentre RCT by Kanovsky et al. (2009) which assessed 214 children (not all BoNT-A naïve) and also found no significant difference in ankle range of motion or Gross Motor Function Measure scores between 4-monthly and 12-monthly injection frequencies.

The lack of consensus regarding re-injection intervals deserves further investigation. In the UK, NICE guidelines (NG145, 2016) advocate no more than two injection sessions in a year period unless used for pain control. Outside the UK, more frequent injections were advocated every 3-6 months in an attempt to arrest contracture development in the younger child (Crownier and Racette, 2008, Dabrowski et al., 2017, Dursun et al., 2018, Molenaers et al., 2001, Strobl et al., 2015). However, there are concerns that more frequent re-injection may be associated with increased incidence of adverse events. Crownier et al. (2010) reported an increased rate of adverse events with 3 monthly re-injection intervals. They recommended extending the re-injection interval to a minimum of six months, in addition to keeping the dose within recommended maximum levels. In the only two RCTs to date of injection frequency in children with cerebral palsy, both studies confirmed that injection of the gastrocnemius-soleus complex for spastic equinus was as effective when performed once per year compared with 3 times per year (every 4 months) (Hastings-Ison et al., 2016, Kanovsky et al., 2009).

1.4.6 Physiological changes in muscle post BoNT-A toxin

Although generally well accepted, BoNT-A remains an invasive treatment for CYPwCP with longitudinal changes in developing muscles not well characterised. There is little published data but emerging evidence shows a structural and mechanical muscle impact following BoNT-A, with indications of long term muscle atrophy. This suggests potential harmful effects and has implications for repeat injections in growing muscle (De Beukelaer et al., 2022, Mathevon et al., 2015).

Researchers have suggested that there may be long term histological changes in both typically developing and spastic muscles following single and multiple injections of BoNT-A (Mathevon et al., 2015, Multani et al., 2019b, Schroeder et al., 2009a). Although BoNT-A has been described as a 'reversible treatment' (Ney and Joseph, 2007), there is increasing evidence to suggest that BoNT-A exposure in CYPwCP may be associated with impaired muscle growth in the short term (Alexander et al., 2018, De Beukelaer et al., 2022, Park et al., 2014, Van

Campenhout et al., 2013, Williams et al., 2013b) and potential long term atrophy (Barber et al., 2013, Fortuna et al., 2013, Van Campenhout et al., 2013).

Studies investigating pathophysiological changes within hypertonic muscle have reported conflicting findings, with both positive and negative results described. However, a variability in measurement techniques and muscles assessed, makes comparison between studies challenging (De Coulon et al., 2022, Eek et al., 2014, Fortuna et al., 2013, Legerlotz et al., 2009, Minamoto et al., 2015, Sim et al., 2012, Tedroff et al., 2009).

Alteration in the visco-elastic properties of the muscle have been reported following BoNT-A. The reported positive effects of treatment have included increased volume of injected muscles, with an associated increased force production and increase in muscle strength. Changes have been associated with improved compliance and extensibility of the target muscle, leading some researchers to argue BoNT-A may result in long term improvement in the function of spastic muscle (Alhusaini et al., 2011, Boyd et al., 2000, Eek and Himmelmann, 2016). However, other studies have shown improvement in gait parameters with no evidence of change in muscle volume following injection (Barber et al., 2013). Conversely, Lee et al. (2021) suggested short-term reduction of muscle mass in children with hemiplegia at 4 weeks following BoNT-A but this was significantly recovered at 12 weeks. Other researchers found has no positive effect on muscle stiffness following BoNT-A with evidence to suggest progressive weakness and reduction in muscle volume following long term use (Kalkman et al., 2020, Park et al., 2014, Pingel et al., 2016, Williams et al., 2013a).

It is widely acknowledged that skeletal muscle fibres are dynamic structures, capable of changing their phenotype following any altered neuromuscular activity. However, there is evidence from animal models, that frequent BoNT-A can result in a change of muscle fibre type (Inagi et al., 1999, Minamoto et al., 2015). There is concern within the field that any alteration in fibre type could be detrimental to growing muscle of CYPwCP, leading a number of researchers to express concern

about potential harmful effects of long term use of BoNT-A (Minamoto et al., 2015, Valentine et al., 2016).

Further work is imperative to investigate the physiological changes on growing muscle; the conflicting evidence and controversy regarding the potentially damaging effect on growing muscle further strengthens the need to introduce meaningful outcomes following BoNT-A to identify the effectiveness of BoNT-A treatment in both short term and long-term use in CYP.

1.4.7 Outcome measures and the ICF

As highlighted, the evidence for effectiveness of BoNT-A appears to be mostly based on short term outcomes (12-16 weeks post injection) and is often related to changes at the impairment level (restriction of body functions and structures). Although there is evidence to recommend BoNT-A as an effective anti-spasticity treatment, its beneficial effects on function, activity and participation remain to be established (Read et al., 2017). Few trials have explored improvement in the activity and participation domains or quality of life after BoNT-A injections (Löwing et al., 2017, Tilton et al., 2017, Wright et al., 2008). Whilst many of these studies refer to statistically significant change following treatment, little reference is made to minimal clinically important differences (MCIDs). The absence of MCIDs makes interpretation of meaningful change for ambulant CYPwCP difficult (Wright et al., 2008).

It remains a challenge to identify responsive outcome measures sensitive to change following BoNT-A, particularly those with an ability to relate change in impairment to change in activity and participation (Baker et al., 2002, Rosenbaum, 2020, Wright et al., 2008). Current research highlights the importance of including outcome measures evaluating activity, participation and QOL to assess response following interventions (Gordon, 2014). It has been suggested that future efficacy assessments of BoNT-A should take into account the impact of the treatment on a child's function and meaningful goals should be set in the context of the CYP's life at home, in school and within the community (Heinen et al., 2021, Nguyen et al., 2016,

NICE, 2012, Tilton et al., 2017). To date few studies have incorporated information about a change in participation or activity level or qualitative data relating to children and families' perception of change post BoNT-A treatment (Wright et al., 2008; Lowing et al., 2010; Tilton et al., 2016; Nguyen et al 2017).

In addition, although it is widely acknowledged that BoNT-A treatment is not a 'stand-alone' treatment, detailed information regarding the adjunctive measures (co-intervention) used in conjunction with BoNT-A is often lacking, making evaluation of its efficacy difficult (Mathevon et al., 2019, Schasfoort et al., 2017, Williams et al., 2012).

1.4.7.1 Quality of movement

There is also a paucity of studies incorporating the opinion of children and families when evaluating the benefits of BoNT-A treatment. Those that have incorporated parental opinion, have reported that families refer to a change in the quality of motor performance in their child when they have observed benefit following BoNT-A intervention. Parents describe an improvement in the ease of movement, co-ordination, and lower limb alignment, reporting an ease and fluidity of movement following injections (Wright et al., 2008). This is in keeping with other qualitative studies following interventions in CP such as Selective Dorsal Rhizotomy (SDR) when improvement in the 'quality' of movement has been observed, and 'quality' was considered more important by parents than the improvement in the 'quantity' of movement (Eliasson et al., 2000)

Quality of movement (QoM) is a significant part of motor performance not usually captured by standardised outcome measures evaluating the efficacy of BoNT-A. Reviews of research in CP have noted a lack of sensitive measures of movement performance which may contribute to the failure to demonstrate treatment effectiveness (Boyce et al., 1991, Wright et al., 2014a). Research suggests that compromised movement quality in CP can limit participation and hinder inclusion (Steenbergen, 2014). Improvement in quality attributes such as alignment, stability and coordination may enhance function and decrease effort (Eliasson et al., 2000,

Janssen et al., 2012). Although an evaluation of change in QoM has been reported following other interventions in CP such as SDR, there appear to be no published studies that have used a standardised measure to evaluate change in quality of movement following BoNT-A.

1.4.7.2 Quality of movement outcome measures

Despite its relevance, objective assessment of movement quality is a complex phenomenon. A review of the literature demonstrates that whilst there are established validated tools to measure QoM in the upper limb in CP such as the Melbourne Assessment (DeMatteo et al., 1993) and the QUEST (DeMatteo et al., 1993), there are few validated outcome measures which attempt to evaluate QoM in the lower limb in CP.

The Gross Motor Performance Measure (GMPM) was developed to evaluate change in gross motor performance over time in CYPwCP. This was introduced to objectively measure QoM and was designed to complement the gold standard tool for evaluating gross motor function in CP the Gross Motor Function Measure (GMFM) (Boyce et al., 1995). Although reliability of the GMPM was good for children with spastic CP (intraclass correlation coefficients, ICC 0.84-0.97) (Boyce et al., 1995, Ko and Kim, 2012), with good evidence of responsiveness and construct validity, there were some limitations with the measure.

The GMPM consists of 20 test items measured across the five dimensions of the GMFM, scored during a child's 'live' performance. A five-point ordinal scale (1-5) is used to evaluate performance against five quality attributes: alignment, coordination, dissociated movement, stability and weight shift. As there were only four test items per dimension, it was perceived that the measure did not provide sufficient detail of QoM. Additionally, complex scoring and lack of specificity of scoring criteria were identified as limitations to using the measure in clinical practice (Wright et al., 2014a).

The Quality Function Measure (QFM) was developed as a new standardised observational measure, designed to evaluate change in gross motor QoM in standing and walking skills in ambulant CYPwCP (Wright et al., 2014a). It is an adaptation of the GMPM and used in conjunction with GMFM-66 dimensions D (Standing) and E (Walking, running and jumping). It incorporates the same five quality attributes with a modified ordinal three-point scoring scale (0-3). Modifications introduced to address the limitations of the GMPM include an increased number of test items (37) which are scored from a video recording of GMFM dimensions D and E and detailed scoring criteria with item specific response options.

The QFM has been validated in ambulatory CYPwCP and has been shown to have excellent reliability ($ICC \geq 0.89$) (Tustin et al., 2016, Wright et al., 2014a). It is able to differentiate scores by GMFCS Level thereby providing evidence of discriminant validity. To date there are no published studies evaluating the responsiveness of the QFM after interventions in CP. However Minimum Detectable Change (MDC) estimates of 9-12% for most attributes have been established (Wright et al., 2014a) and indicate that the QFM may be useful for evaluative purposes. The different QFM attributes provide an opportunity to study relative change in attribute scores following interventions in CP.

The QFM could be a valuable tool in the evaluation of the efficacy of BoNT-A treatment, particularly as families often describe a change in movement quality and ease of movement following injections. The use of a standardised objective measure would allow clinicians to evaluate any change in the 'quality' of motor performance as well as the 'quantity' of motor performance as measured by other standardised measures.

1.5 Summary

Although considered an established treatment modality, this outline of the literature has illustrated that there are deficits in the knowledge base regarding the use of BoNT-A. Results from trials evaluating effectiveness are mixed, often

involving small numbers and as a result may lack generalizability. There is a lack of consensus regarding the optimal age range for BoNT-A treatment, frequency of re-injection and length of treatment before other management options for hypertonia are sought for CYPwCP

There appears to be little evidence in the literature to date relating a change at impairment level directly with improvement in activity, participation and patient and family reported quality of life following BoNT-A. There are concerns that the standardised outcomes currently used to measure change remain focused on impairment measures and that activity outcome measures used, such as GMFM, due to ceiling effects, may not be sensitive enough to pick up subtle changes following treatment. As such they are limited in their ability to identify meaningful change and may be unable to differentiate between those children who do well with injections and those children for whom continued treatment with BoNT-A may not be indicated. Changes over time in these measures are not well characterised and there is concern that in the absence of MCIDs, outcome measures may not reflect clinically significant change post intervention. As a result, evidence that BoNT-A is effective in making an impact in these areas is elusive.

Qualitative data relating CYPwCP and their caregiver's perception of change post BoNT-A is also lacking. Despite a number of studies incorporating CYP and parent opinion as a secondary outcome measure, CYP experience and that of their families is rarely reported in the existing literature (Wright et al., 2014, Thomas et al., 2014, Lowing et al., 2017). Interest in patients' perspectives and the concept of patient-centred care has grown with our understanding that the impact of interventions is more meaningfully assessed using patient-based outcome measures. The perspective of CYP and their families are important not only before treatment but also during the rehabilitation period after BoNT-A to allow the incorporation of their 'values and preferences' during the process of clinical decision making (Tilton et al., 2017).

Despite recognition in the literature of a need to investigate long term effects of repeated BoNT-A use, conflicting evidence exists, with both positive and negative effects reported in relation to histological changes in the muscle. There are obvious clinical implications for CYP receiving BoNT-A, not only regarding the contested longitudinal effects in growing muscle but also regarding the administration of BoNT-A. Children receive injections under sedation, which despite local analgesia can cause discomfort with multiple muscle groups injected at the same time. The burden on the family also needs to be considered with days off from school and work to attend hospital appointments as well as the financial implication for the NHS.³

Concern has been raised that BoNT-A treatment may be overprescribed for CYPwCP with little guidance about which patients will benefit; suggesting potential harm if clinical outcomes are unclear (Gough, 2009, Sim et al., 2012). However, clinical evidence suggests that in the right patient group, at the right time, BoNT-A remains a valuable treatment option. There is a necessity to develop clear guidelines and treatment algorithms in order to advise clinicians and families about which CYP are most likely to benefit from this intervention.

As can be seen from this brief literature review, there are gaps in the literature about the effects of BoNT-A treatment beyond the short term, and a lack of information about outcomes in the domains of the ICF other than Body structure and Function, particularly outcomes evaluating change in Activity and Participation, which have been described as meaningful to children and families. In order to investigate this further, the following chapter contains a detailed systematic review of existing literature which has evaluated the efficacy of BoNT-A by assessing outcomes within all of three domains of the ICF; Body structure, Activity *and* Participation.

³A day case admission for BoNT-A treatment costs in excess of £1000 plus the additional cost of pre and post injection assessment appointments.

Chapter 2 Systematic Review

Do lower limb Botulinum Toxin A injections have an impact on impairment, activity limitation and participation restriction in ambulant children (GMFCS I-III) with cerebral palsy? A systematic review across the ICF domains.

2.1 Introduction and background

The International Classification of Functioning Disability and Health, commonly referred to as the ICF, is a classification of health and health-related domains. It was established by the World Health Organisation (WHO) over twenty years ago in 2001 and is based on the bio-psycho-social model of functioning, disability, and health. In 2007 it was further modified with the introduction of the ICF -Child and Youth model (ICF-CY), which aimed to provide a similar framework for health and disability in children (Figure 2-1). Since this time the scientific community has been encouraged to think about evaluating the efficacy of interventions aimed at children and young people in meaningful terms based on measuring outcomes throughout the different domains of the ICF (Rosenbaum, 2021b).

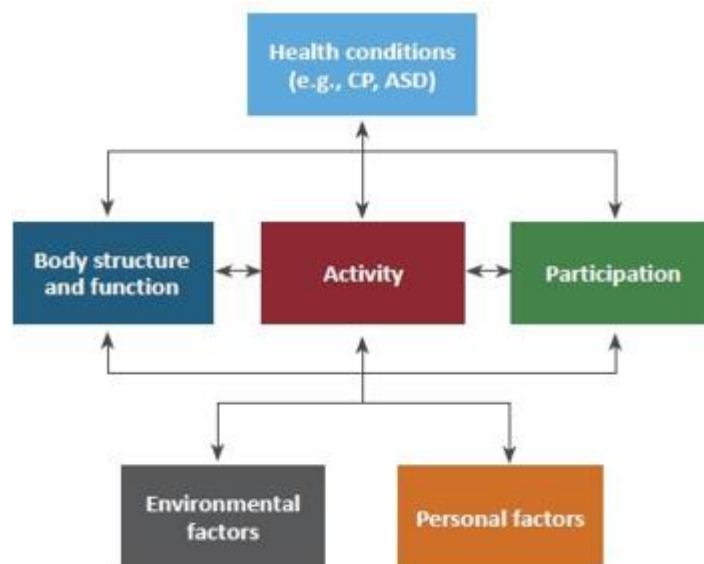


Figure 2-1 International Classification of Functioning Disability and Health, (ICF)(WHO, 2007)

BoNT-A is well recognised as an anti-spasticity treatment in the management of children with CP. However despite its widespread use, the effects on function,

activity and participation still remain to be established (Read et al., 2016, Reedman et al., 2017). There is currently little evidence to relate improvement at impairment level (body function and structure) with a change in other domains of the ICF, such as activity, participation, and health related quality of life (HrQoL) (Sim et al., 2012) in ambulant children and young people with CP (CYPwCP) following lower limb BoNT-A injections. The majority of research consists of short term (12-16 weeks) follow up reports related to body structure and function and activity.

This chapter presents a systematic review of the impact of lower limb BoNT-A injections across the ICF domains, namely body structure and function, activity and participation in ambulant CYPwCP (defined as Gross Motor Function Classification System (GMFCS) levels I-III) (Palisano et al., 1997). The review was conducted according to the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.2 Method

2.2.1 Search Strategy

2.2.1.1 Information sources

Prior to conducting this review, the International Prospective Register of Systematic Reviews (PROSPERO) and *Cochrane Database of Systematic Reviews (CDSR)* were searched for existing systematic review protocols on the use of BoNT-A in CP to ensure that a systematic review on this topic 'evaluating the effects of lower limb BoNT-A throughout all the domains of the ICF' had not previously been registered. A detailed protocol for the proposed review was developed and registered online (CRD42019138523). The search strategy was developed according to the Population, Intervention, Comparison, Outcomes and Study (PICOS) approach (Moher et al., 2009). A bank of relevant search terms was developed using Medical Subject Headings (MeSH) where possible and a search strategy for PubMed was drafted by the researcher with input from a health research librarian.

Articles were identified using the key word combinations of Cerebral Palsy and Botulinum Toxin A. Keywords were matched to the Medical Participant Headings Index and explored or searched as keywords where appropriate (see Medline search for detailed search strategy Appendix 14.9.2).

Six electronic databases were searched: SCOPUS; CINAHL; MEDLINE; EMBASE; COCHRANE; and WEB OF SCIENCE. Additional searches were carried out on the grey literature. This included conference proceedings from 2007 to 2022, specifically from annual meetings of the American Academy for Cerebral Palsy and Developmental Medicine, European Academy of Childhood Disability and Australasian Academy for Cerebral Palsy and Developmental Medicine. The last updated search was performed on 15th July 2022.

2.2.1.2 Types of study included

Original research examining the use of BoNT-A in ambulant children and young people with cerebral palsy (GMFCS I-III) were assessed. Only studies that measured therapeutic effect within three domains of the WHO's ICF - Body Structure and Functions, Activity and Participation (WHO, 2007) - were included. Study designs included randomized controlled trials; quasi-randomized controlled trials; prospective pre-post studies; cohort studies with and without a concurrent control group; and case series with a minimum of ten participants ($n \geq 10$). Previous systematic reviews and meta-analyses were excluded but searched to ensure relevant articles were included. Articles were excluded if they were reviews, letters, conference abstracts without complete data or commentaries.

2.2.1.3 Condition

Cerebral palsy

2.2.1.4 Population

The search included *ambulant* children and young people between the ages of 2-18 years who had been clinically diagnosed with cerebral palsy (as classified by GMFCS I-III). There were no restrictions on gender, race, or nationality.

2.2.1.5 *Intervention*

Lower limb intra-muscular Botulinum neurotoxin A (BoNT-A) injections

2.2.1.6 *Comparator*

Comparators of interest in this review were:

- No intervention
- Standard or usual care
- Additional therapy (e.g., casting, training programmes)

2.2.1.7 *Outcome*

Studies were included if they reported continuous outcomes related to all three ICF domains of body function and structure, activity, *and* participation, measured using a valid or clinically accepted outcome measure for CYPwCP.

2.2.1.8 *Timing*

Studies published from 2007 onwards were eligible for inclusion due to the introduction of ICF-Children and Youth version (ICF-CY) in 2007. Studies were included if the length of follow up after BoNT-A administration exceeded 4 weeks to allow the target threshold (reduction in dynamic spasticity) of BoNT-A injections to be reached.

2.2.1.9 *Setting*

There were no restrictions based on study setting.

2.2.1.10 *Language*

Studies were included if they were published in the English language only (due to a lack of resources available for translating).

The inclusion and exclusion criteria are summarised in Table 2-1.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Children aged between 2 and 18 years • Confirmed diagnosis of ambulant cerebral palsy (GMFCS level I-III) • Lower limb intra-muscular Botulinum Toxin A administration (alone or in combination with additional therapy such as casting, FES, targeted training programs etc). • Any original clinical studies with a measurement of the therapeutic effect of BoNT-A with n≥10 participants • Therapeutic effect post BoNT-A included outcomes of activity <i>and</i> participation in addition to impairment outcome • Full text publication in English 	<ul style="list-style-type: none"> • Participants without a confirmed diagnosis of CP • The ambulatory level of the study participants was not described • Studies with participants from all GMFCS Levels I-V where relevant data from GMFCS level I-III could not be separated • Upper limb BoNT-A only or studies with participants with mixed upper and lower limb injections where results from lower limb injections could not be separated • Studies investigating effects of BoNT-A for non-motor problems such as drooling or bladder instability only • Studies describing only the pathophysiology or histological effects of BoNT-A with no measurement of therapeutic outcome • Studies describing administration techniques of BoNT-A, side effects profile with no measurement of therapeutic outcome • Length of follow up following injections less than 4 weeks • No full text available, abstract-only articles (books, conference, letters), systematic reviews and meta-analyses. • Studies with a publication date prior to 2007

Table 2-1 Inclusion and exclusion criteria for articles included in the systematic review

2.2.2 Data extraction, selection, and coding

Following duplicate removal, the title and abstract of 2086 titles were screened independently by two reviewers (the researcher, LK and Clinical supervisor, LC), to identify articles for inclusion using the predefined eligibility criteria shown in Table 2-1. Abstracts meeting inclusion criteria or those requiring the full text to clarify inclusion were retained and reviewed independently by the researcher (LK) and supervisor (LC)⁴. Reference lists of included articles were also reviewed for additional literature not identified using the search strategy. Backward and forward citation chasing was carried out to help confirm the saturation of the initial searches. Each step of the selection process is outlined in a PRISMA-style flow chart in Figure 2-2. Consensus was reached by discussion between the two researchers and although articles could be referred to an independent expert (BC)⁵ if required, there were no disagreements.

The full text publications that met inclusion criteria were reviewed by two researchers (LK/LC). Two study authors (Balgayeva et al., 2018, Kelly et al., 2019) were contacted for clarification and additional information to inform study selection. Summary data of each included article were extracted independently by two researchers (LK/LC). When there were studies with more than one publication, reports were compared and the publication with the most complete data was used. Disparities were resolved by discussion and consultation with the wider review team. Any disagreement was resolved through discussion and although an independent expert (BC) was available to arbitrate, this was not required.

2.2.2.1 Strategy for data extraction

Microsoft Excel data extraction tables specifically designed by the researcher were used to record the following descriptive details:

1. Participants: study setting; study population and participant characteristics.

⁴ LC- Dr Lucinda Carr Clinical academic supervisor

⁵ BC- Dr Belinda Crowe Independent expert

2. Study: date of publication; country of origin; sample size; study type; length of study.
3. Intervention; BoNT-A type (BOTOX, Dysport etc.), dose-including dilution details, administration (e.g., ultra-sound guidance) safety outcomes, sedation protocols, number of injections, injection frequency including BoNT-A naive or repeat injection, muscles injected.
4. Adjunctive therapy used including details of usual care and reference to treatment fidelity and adherence to planned treatment.
5. Outcome measures used: categorised relative to the ICF domains; number of items; description of the items; method of administration; interpretation and summary scoring.

2.2.2.2 Analysis

A narrative approach was used to synthesize the data and present the main findings. A meta-analysis was planned but was not possible due to the variation in study characteristics, outcome measures, data collection methods, and an inconsistency in reporting of outcomes. Each eligible study for inclusion in the review was summarised and described in terms of its participants, interventions, and outcomes. The effects of BoNT- A on the ICF Domains of body structure and function, activity and participation were reviewed.

2.2.2.3 Quality assessment

Critical appraisal of the included studies was performed using the American Academy for Cerebral Palsy and Developmental Medicine's (AACPD) methodology for conducting systematic reviews (group design studies) and the AACPD Treatment Outcomes Committee (TOC) conduct tool was used to assess quality (see Appendix 14.9.5 (Darrah et al., 2008)).

The AACPDM (TOC) framework analyses and categorizes treatment outcomes from studies according to the components of the ICF (WHO, 2007), and judges the strength of the evidence from each article according to the study design and the researchers' rigor in the conduct of the study. The levels of evidence of the included studies were determined with the Sackett levels of evidence modified by AACPDM (Darrah et al., 2008). The quality conduct tool was modified specifically for this review to include conduct evaluation of Level IV studies.

Two reviewers (LK/LC) assessed the methodological quality of the studies independently without blinding to authorship or journal. There was only one discrepancy (Schasfoort et al., 2018) and this was resolved between the two researchers, without the need to involve the independent expert (BC).

2.3 Results

2.3.1 Data extraction

The PRISMA group (Moher et al., 2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses was followed. The initial searches resulted in 4088 studies. After duplicates were removed 2086 titles and abstracts were screened. Of these, 82 publications met initial selection criteria and were retrieved for full text review. The number of articles included and reasons for exclusion are provided in Figure 2-2.

A total of 11 publications met the final inclusion criteria and were included in the review (Table 2-2). Studies included 5 RCTs; 2 double blind RCTs (Bjornson et al., 2007, Delgado et al., 2016b) and 3 single blind RCTs (Hastings-Ison et al., 2016, Kelly et al., 2019, Thomas et al., 2016), a prospective cohort study (Valentine et al., 2020b), a cross comparison clinical trial (Williams et al., 2013a) and a pragmatic partially randomized single blind multicentre trial (Schasfoort et al., 2018). The remaining three studies were one group pre-post studies (Löwing et al., 2017, Wright et al., 2008, Yap et al., 2010). Agreement between reviewers was 98% for screening by title and 100% for abstract and full text review.

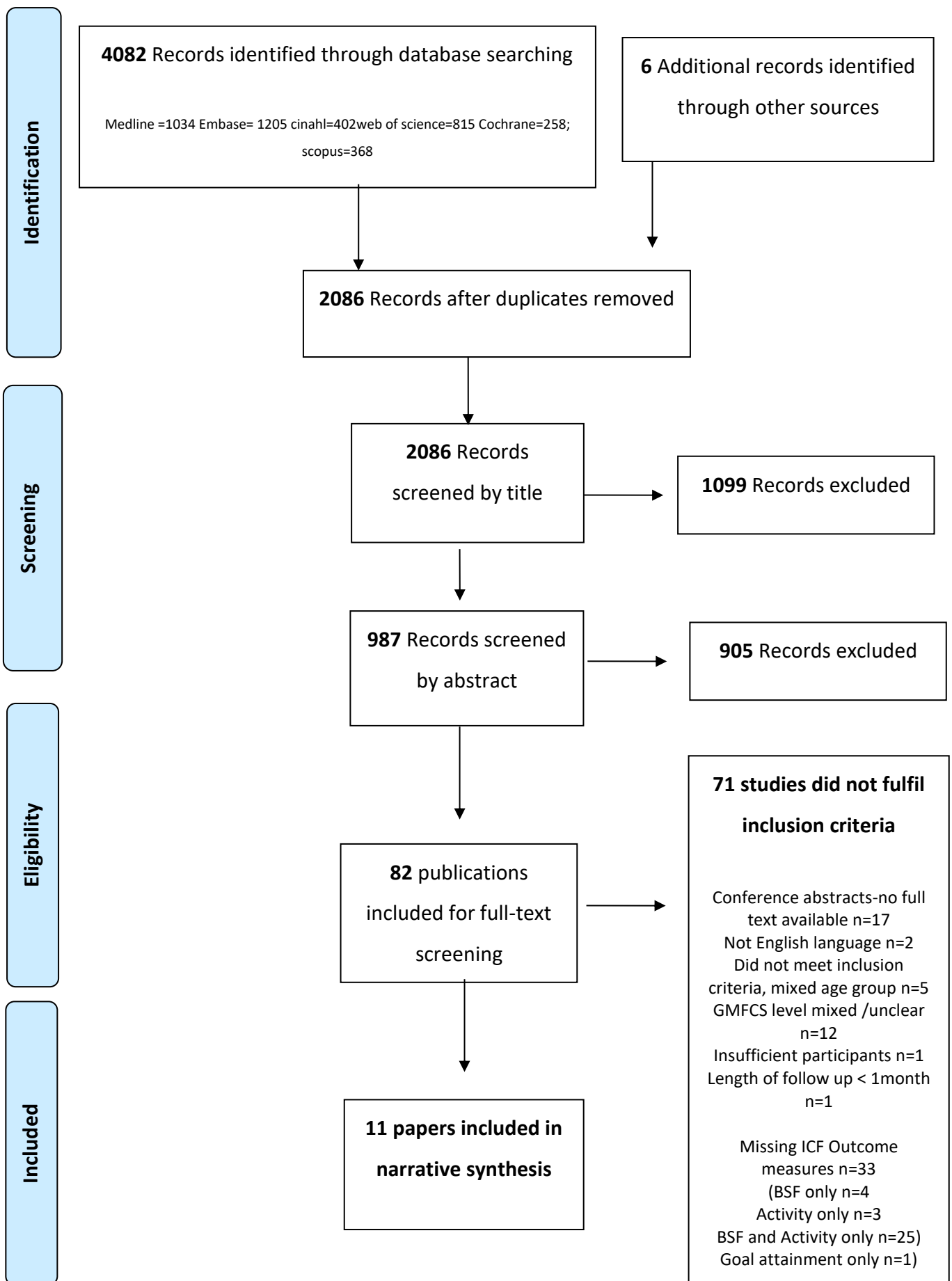


Figure 2-2 PRISMA style flowchart of BoNT-A Studies in Children with CP

Table 2-2 Summary of included studies

Authors	Title	Aim of Study	Method/Design	Sample Total number of participants GMFCS Level	Intervention Length of follow up	Level of evidence
Bjornson et al. (2007)	Botulinum Toxin for spasticity in children with cerebral palsy A: comprehensive evaluation	To evaluate the effects of BoNT-A injections into gastrocnemius muscle in children with spastic diplegia Across all 5 domains of NCMRR domains of medical rehabilitation	Randomised double blinded placebo controlled trial	N=33	BoNT-A vs placebo 24 weeks	II
				GMFCS I n=12		
				GMFCS II n=15 GMFCS III n=6		
Delgado et al.(2016)	AboBotulinumtoxinA for equinus foot deformity in cerebral palsy: A randomised controlled Trial	To prospectively assess the efficacy and safety of one BoNT-A formulation (Dysport)at two doses 15 U/kg/leg (ABO ₁₅) and 10 U/kg/leg (ABO ₁₀) compared with placebo in children with spasticity associated with CP	Randomised double blinded placebo controlled trial	N=235	Two doses of BoNT-A vs placebo 12 weeks	I
				GMFCS I n=131		
				GMFCS II n=78 GMFCS III n=26		
Hastings-Ison et al. (2016)	Injection frequency of Botulinum Toxin A for spastic equinus: a randomised clinical trial	To compare two BoNT-A frequency regimens, 12-monthly vs 4-monthly for spastic equinus in a randomised clinical trial	Randomised clinical trial	N= 42	BoNT A 12-monthly vs BoNT-A 4-monthly 26 months	II
				GMFCS I n=20		
				GMFCS II n=19 GMFCS III n=3		

Kelly et al. (2019)	Casting protocols following BoNT-A injections to treat spastic hypertonia of Triceps surae in children with CP and equinus gait: A randomised controlled Trial	To study the effects of single vs serial casts post BoNT-A for a trial of post BoNT-A casting to treat equinus gait in CP	Randomised controlled trial	N=20 GMFCS I =17 GMFCS II=3	Comparison of two casting protocols + BoNT-A 24 weeks	II
Lowing et al. (2017)	Effects of Botulinum Toxin-A and goal directed physiotherapy in children with CP GMFCS levels I & II	To evaluate short- and long-term effects of Botulinum Toxin-A combined with goal directed physiotherapy in children with CP	Prospective observational Repeated measures study No Control group	N=40 GMFCS I =24 GMFCS II =16	BoNT-A and Goal setting 24 months	IV
Schasfoort et al.(2018)	Intramuscular Botulinum Toxin prior to comprehensive rehabilitation has no added value for improving motor impairments, gait kinematics and goal attainment in walking with spastic cerebral palsy	To compare the effectiveness of BoNT-A plus a 12-week period of comprehensive rehabilitation with comprehensive rehabilitation alone.	Single-blind Partly randomized Multi-centre pragmatic trial	N=65 GMFCS I =19 GMFCS II=23 GMFCS III=23	BoNT-A + Comprehensive Rehabilitation (CR) Vs Comprehensive Rehabilitation alone 24 weeks	III
Thomas et al. (2016)	Evaluation of group versus individual physiotherapy following lower limb intramuscular Botulinum Toxin A injections for ambulant children with CP: A single blind randomised comparison trial	To evaluate efficacy of group versus individual physiotherapy programmes following BoNT-A injections	Single blind Randomised clinical trial	N=34 GMFCS I =14 GMFCS II=13 GMFCS III=7	BoNT-A + Group Physiotherapy Sessions vs BoNT-A +individual Physiotherapy Sessions 26 weeks	II

Valentine et al. (2020)	A prospective study investigating gross motor function of children with cerebral palsy and GMFCS level II after long term Botulinum toxin A use	To evaluate whether children treated at a young age with repeated BoNT-A within an integrated comprehensive service maintain their functional gains at a later age	Prospective observational cohort study	N=28 GMFCS II=28	BoNT-A and GMFCS II stability	IV
Williams et al. (2013)	Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength	To investigate the combination of effects of strength training and BoNT-A on muscle strength and morphology on children with CP	Prospective cross-comparison design clinical trial	N=15 GMFCS I GMFCS II	BoNT-A + muscle training 26 weeks	III
Wright et al. (2008)	How do changes in body functions and structures, activity and participation relate in cerebral palsy?	To investigate how changes in body functions and structures, activity and participation relate following BoNT -A injections in ambulant children with CP	Prospective observational one group repeated measures study	N=35 GMFCS I =11 GMFCS II=12 GMFCS III=12	BoNT-A injections Before and after study 26 weeks	IV
Yap et al. 2010	Determinants of responsiveness to botulinum toxin, casting and bracing in the treatment of spastic equinus in children with CP	To determine whether specific intrinsic (age pattern of CP, child's motivation)and extrinsic (number of treatments, parenting stress) characteristics are associated with responsiveness to BoNT-A injections in children with CP 3 months after injection into the gastrocnemius muscle	Prospective Observational Single group study	N=31 GMFCS I =28 GMFCS II=0 GMFCS III=3	BoNT-A injections Before and after study 12 weeks	IV

2.3.2 Participant and study characteristics

All eleven studies included were prospective studies investigating the effects of BoNT-A injections into lower limb muscles. The demographic characteristics of the study populations are shown in Table 2-3. Three studies reported injections into the calf muscles (gastrocnemius-soleus complex) only (Bjornson et al., 2007, Delgado et al., 2016b, Yap et al., 2010), whilst the remaining eight studies described injections into multiple lower limb muscles (Hastings-Ison et al., 2016, Kelly et al., 2019, Löwing et al., 2017, Schasfoort et al., 2018, Thomas et al., 2016, Valentine et al., 2020b, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010). Only one study did not specify the lower limb muscles injected (Thomas et al., 2016). Outcome measures used within the included studies to evaluate the effectiveness of BoNT-A treatment throughout the domains of the ICF are summarised in Figure 2-3.

The GMFCS was used to classify gross motor functional abilities of the participants who were all ambulant children with spastic cerebral palsy (GMFCS Levels I-III), presenting with either unilateral or bilateral involvement (Cans et al., 2002). Six studies evaluated response in children within GMFCS levels I, II and III (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016, Schasfoort et al., 2018, Thomas et al., 2016, Wright et al., 2008). In the remaining studies, three evaluated GMFCS levels I and II alone (Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a), one study evaluated children from GMFCS Levels I and III, although only three of the 31 participants were classified as GMFCS level III (Yap et al., 2010) and one study involved participants from only GMFCS level II (Valentine et al., 2020b). Only one study (Williams et al., 2013a), did not specify the number of children within each of the GMFCS levels I and II studied. It is of note that participants from GMFCS levels I and II made up 91% of the total number of children studied within this review.

The eleven studies incorporated a total of 938 participants, with a large variability in the number of participants across the different studies (range 15- 235). Participants were aged between 2 years and 17 years (range of means 3.6 years to 10.9 years).

Only one study did not specify the gender of participants (Valentine et al., 2020b), in the remaining studies 61.5% of participants were female.

Four trials compared BoNT-A and usual care (this consisted of the usual therapy care package provided without specific modifications for the purposes of the study). One study was a placebo-controlled trial (Bjornson et al., 2007) and three had a single group design without a control group (Löwing et al., 2017, Wright et al., 2008, Yap et al., 2010). Three trials looked at specific co-intervention packages in association with lower limb BoNT-A injections, these were: BoNT-A plus two casting regimens (single vs serial casting)(Kelly et al., 2019); BoNT-A plus two strengthening regimens (pre and post injection)(Williams et al., 2013a); and BoNT-A plus two physiotherapy (PT) intervention methods (group vs individual therapy sessions)(Thomas et al., 2016). One study compared intensive physiotherapy in two groups with the addition of BoNT-A injections as the intervention (BoNT-A plus intensive PT vs intensive PT alone) (Schasfoort et al., 2018). Two trials looked specifically at BoNT-A administration details; Hastings-Ison et al compared the outcome of BoNT-A injections between two injection frequencies (4 monthly vs yearly) in a single blind controlled trial (Hastings-Ison et al., 2016) and Delgado et al. in a double-blind placebo-controlled trial investigated two different doses of BoNT-A compared to placebo (Delgado et al., 2016b). The remaining study was a longitudinal cohort study which explored the stability of GMFCS level II children following long term use of lower limb BoNT-A injections (Valentine et al., 2020b).

Funding was declared in all but one study (Löwing et al., 2017). Of the remaining studies; one was funded by the pharmaceutical company Ipsen Biopharmaceuticals, Inc (Dysport® (AbobotulinumA toxin) (Delgado et al., 2016b) and two studies received unrestricted educational grants from the pharmaceutical company Allergan Inc. Valentine et al. (2020b) used the funding to complete participant outcome tests and Bjornson et al. (2007) were provided with the BoNT-A product BOTOX® (OnabotulinumA toxin) used in their study. All other studies were funded through national research grants.

The follow up time following BoNT-A injections varied between 12 weeks and 24 months and was clearly stated in all studies with the exception of Valentine et al. (2020b), who followed a cohort of children from birth years 2000-2009 and evaluated outcome in children aged 8-16 years. The follow up time in this latter study was unclear. For the basis of this review short term response following BoNT-A has been classified up to six months and long term six months and over.

The details of BoNT-A administration were described to different extents within the studies. (Methodological details including product characteristics, dose and muscles injected and specific administration details have been summarised in Appendix 14.9.6. Two BoNT-A products were used, BOTOX® (OnabotulinumtoxinA – Allergan Inc.) and Dysport® (AbobotulinumtoxinA - Ipsen Biopharmaceuticals, Inc). BOTOX® was used in all the studies apart from the largest RCT by Delgado et al. (Delgado et al., 2016b). Mean dosage was described in all studies except for Thomas et al. (2016) who described general administration in line with 'WE Move Inc' published guidelines (Brin, 1997). Four studies described administration details of the injections using EMG or ultrasound guidance (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016, Löwing et al., 2017) and sedation details were provided in six of the eleven studies (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016, Löwing et al., 2017, Schasfoort et al., 2018, Yap et al., 2010).

The majority of studies described the outcome following a single injection cycle (Bjornson et al., 2007, Delgado et al., 2016b, Kelly et al., 2019, Schasfoort et al., 2018, Thomas et al., 2016, Wright et al., 2008, Yap et al., 2010), with multiple injection cycles reported in three studies (Hastings-Ison et al., 2016, Löwing et al., 2017, Valentine et al., 2020b). Two of the studies consisted of participants receiving BoNT - A injections for the first time (BoNT-A naïve) (Bjornson et al., 2007, Hastings-Ison et al., 2016) and six studies had a combination of BoNT-A naïve participants and those with a variable number of previous injection cycles (Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Schasfoort et al., 2018, Wright et al., 2008, Yap et al., 2010). One study consisted of participants who had all received

previous injections (Valentine et al., 2020b) and in the remaining study by Thomas et al. (2016) previous injection history was not provided.

All studies, as per review inclusion criteria, had outcomes measured in ICF domains of Body function and structure, Activity and Participation. Four studies used additional measures to capture behavioural components of the ICF such as quality of life (Hastings-Ison et al., 2016, Kelly et al., 2019, Thomas et al., 2016), child motivation and parenting stress (Yap et al., 2010). Forty-three different outcome measures were used within the 11 studies. (These are summarised in Figure 2-3). Detailed information about the outcome measures according to ICF domains, demographics of included studies and outcomes used are found in Table 2-3.

Figure 2-3 Outcome measures used in the included studies within their ICF domains



KEY: AOC, Angle of Catch; AROM, Active range of motion; COPM, Canadian Occupational Performance Measure; CHQ, Child Health Questionnaire; DTR, Deep Tendon Reflexes; DMQ, Dimensions of Mastery Questionnaire; EVGS, Edinburgh Visual Gait Scale; ECI, Energy Cost Index; FAQ, Gillette Functional Assessment Questionnaire; GAS, Goal Attainment Scaling; GDI, Gait Deviation Index; GMFCS, Gross Motor Function Classification System; GMFM(-66), Gross Motor Function Measure (66); GPS, Gait Profile Score; I, intervention; 3DGA, 3 dimensional Gait analysis; MAS, Modified Ashworth Scale; MTS, Modified Tardieu Scale; MVT, maximum voluntary torque; OGS, Observational Gait Scale; PEDI, Pediatric Evaluation of Disability Inventory; PODCI, Pediatric outcomes data collection instrument; PROM, passive range of motion; PRS, Physician's Rating Scale; PGA, Physicians Global Assessment Scale; PSI-SF, Parenting Stress Index-Short Form; QEK, Quantitative EMG Kinesiology; RCT, randomised control trial; ROM, Range of motion; SCALE, Selective Control Assessment of the Lower Extremity SMC, selective muscle control; SMS, Total and elastic path length-measurement of spasticity; STS, sit to stand; TS Tardieu Scale; WeeFIM, Pediatric Functional Independence Measure; VAS, visual analogue scale.

Table 2-3 Demographics of included studies and outcomes used

Study	Participants (Male Female)	Age Range Mean age years (SD)	Clinical Type of CP	GMFCS Level	Intervention	Outcomes measured in ICF Domains Body Structures and Function, Activity & Participation (* Primary outcome measure)
Bjornson et al. (2007)	N=33 Intervention (I) group n=17 (12 M, 5 F) GMFCS I/II/III: 8/7/2 Control (C) group n=16 (6 M, 10 F) GMFCS I/II/III: 4/8/4	3-12 years I = 5.4 (2.1) C = 5.6 (2.5)	Spastic Diplegia	GMFCS I n=12 GMFCS II n=15 GMFCS III n=6	BoNT-A vs placebo 24 weeks	BSF: Muscle Tone and spasticity; SMS*; MAS; Clonus; DTR, QEK, MVT, Ankle ROM (PROM), ECI Activity: GMFM (88 & 66*) Participation: COPM -Performance COPM-Satisfaction /Goal Attainment Scaling (GAS)
Delgado et al. (2016)	N=235 (ITT 241/ 226 completed) Abo 10 group n =79 (ABO ₁₀) (45M, 34 F) GMFCS I/II/III: 48/24/9 Abo 15 group n=79 (ABO ₁₅) (48 M, 31 F) GMFCS I/II/III: 45/24/10 Control group n=77 (48 M,29 F)GMFCS I/II/III: 40/30/7	2-17 years Abo 10 group 6.0 (3.3) Abo 15 group 5.7 (3.2) Control group 5.9 (3.5)	Spastic Hemiparesis Diparesis Tetraparesis	GMFCS I n=131 GMFCS II n=78 GMFCS III n=26	Two doses of BoNT-A vs placebo 12 weeks	BSF: Muscle tone and spasticity: MAS*; Tardieu Scale (TS) Activity & function: PGA Participation: Participation & ADL: GAS
Hastings-Ison et al. (2016)	N=42 12 monthly (13 M,8 F) GMFCS I/II/III: 11/8/2 4 monthly (10 M, 11 F) GMFCS I/II/III: 9/11/1	2-5 years 12 monthly 3.6 (1.1) 4 monthly 3.6 (1.2)	Spastic Diplegia Hemiplegia	GMFCS I n=20 GMFCS II n=19 GMFCS III n=3	BoNT A 12- monthly vs BoNT- A 4-monthly 26 months	BSF: PROM Ankle* using an instrumented measure Activity & function: 3DGA, FMS Function & Participation: FAQ HRQOL: CHQ
Kelly et al. (2019)	N= 20 Serial casts Group n=10 (5M, 5F) GMFCS I/II: 8/2 Single cast group n=10 (4 M, 6F) GMFCS I/II: 9/1	2-7 years Serial 5.4 (1.6) Single 4.8 (1.7)	Hemiplegia Diplegia Triplegia	GMFCS I =17 GMFCS II= 3	Comparison of two casting protocols + BoNT- A 24 weeks	BSF: Muscle Tone and spasticity: MTS* MAS (6 point scale), PROM Activity & function: Gait: GAITRite, TM GMFM-66 Participation: PEDI QOL: CPQOL
Lowing et al. (2017)	N=40 (36 patients completed study) (17M, 23 F)	4-12 years Mean age 6.4 years (2.0)	Unilateral Bilateral	GMFCS I =24 GMFCS II =16	BoNT-A and Goal setting 24 months	BSF: Muscle Tone and spasticity: MAS, Ankle ROM (PROM), SMC Activity & Function: 3D Gait analysis and GDI* Activity & Participation: GAS
Schasfoort et al. (2018)	N=65 Unilateral=14 Bilateral =51 (37 M,28 F) Intervention group=-41 (22M, 19 F) GMFCS I/II/III: 12/13/16 Comparator group =24 (15 M, 9 F) GMFCS I/II/III: 7/10/	4-12 years Mean age 7.3 years (2.3) I=7.5 (2.4) C=6.9 (2.3)	Spastic CP Unilateral Bilateral	GMFCS I =19 GMFCS II=23 GMFCS III=23	BoNT-A + CR Vs CR alone 24 weeks	BSF: Muscle Tone and spasticity: AoC (MTS R1 equivalent), Pain VAS, STS, ROM, and PROM (MTS -R2) Activity: 2D Gait analysis with spatio-temporal data Participation: GAS Parent reported functional outcome(VAS)

Thomas et al. (2016)	N=44 (41 completed: 2 dropped out of IND; 1 GRP) GRP= 17 (13 M,4 F) GMFCS I/II/III: 5/8/4 Unilateral/bilateral (GRP):7/10 IND=17 (11 M,6 F) GMFCS I/II/III: 9/5/3 Unilateral/bilateral (IND):5/12	4-14 years GRP = 7.7 (2.0) IND =8.6 (2.0)	Spastic CP Unilateral Bilateral	GMFCS I =14 GMFCS II=13 GMFCS III=7	BoNT-A + GRP Vs BONT-A + IND Physiotherapy 26 weeks	BSF: Functional balance: PRT Activity: EVGS*, 1MFWT, GMFM 88 Participation: COPM* QOL: CPQOL
Valentine et al. (2020)	N=28 (convenience sample of 40 eligible) Diplegia =15 Hemiplegia =13 No details given regarding M/F	8-16 years Median age (IQR) 10.9 years (10,11.8)	Diplegia hemiplegia	GMFCS II=28	BoNT-A & GMFCS level stability	BSF: Pain the Brief Pain inventory Activity: GMFM-66 Participation: PEM-CY
Williams et al. (2012)	N=15 Pre -training n=7 (3M,4F) Post training n=8 (5M,3 F)	5-11 years Mean age 8.42 years (1.83) Pre-training= 8.17 years (1.75) Post training= 8.25 years (0.17)	Spastic diplegia	GMFCS I GMFCS II =15 (No specified detail)	Pre and Post BoNT-A strengthening programme 26 weeks	BSF: Spasticity MAS, selective control SCALE, muscle strength (dynamometer), muscle volume with MRI Activity & Participation: Goal attainment with GAS
Wright et al. (2008)	N=35 (19 M, 16F) Hemiplegia = 7 Diplegia=28	3-12 years Mean age 5.5 years (2.2) Age strata < 6 years =23 > 6 years= 12	Spastic Diplegia Hemiplegia	GMFCS I =11 GMFCS II=12 GMFCS III=12	BoNT-A before and after outcome measures 26 weeks	BSF: Spasticity assessed with MTS* Activity & function: timed walk test over 20 metres, D& E dimensions of GMFM, GMFM-66 Participation: PEDI, PODCI
Yap et al. (2010)	N=31 (17M, 14 F) Hemiplegia =22 Diplegia =9	< 18 years Mean age 6.3 years (2.10)	Spastic Diplegia Hemiplegia	GMFCS I= 28 GMFCS II= 3	BoNT-A before and after outcome measures 12 weeks	BSF: AROM and PROM (dorsiflexion)and spasticity assessed with MAS (6 point scale) Activity & function: FAQ, Gait modified PRS, GMFM-66 Participation WeeFIM Personal Factors: Parental stress: PSI-SF Child's motivation: DMQ

KEY: AOC, Angle of Catch; AROM, Active range of motion; BoNT-A, botulinum toxin type A; COPM, Canadian Occupational Performance Measure; CHQ, Child Health Questionnaire; DTR, Deep Tendon Reflexes; DMQ, Dimensions of Mastery Questionnaire;EVGS, Edinburgh Visual Gait Scale; ECI, Energy Cost Index; FAQ, Gillette Functional Assessment Questionnaire; GAS, goal attainment scaling; GDI, Gait Deviation Index; GMFCS, Gross Motor Function Classification System; GMFM(-66), Gross Motor Function Measure (66); GPS, Gait Profile Score; I, intervention; 3DGA, 3 dimensional Gait analysis: MAS, Modified Ashworth Scale; MTS, Modified Tardieu Scale; MVT, maximum voluntary torque; OGS, Observational Gait Scale; PEDI, Pediatric Evaluation of Disability Inventory; PODCI, Pediatric outcomes data collection instrument; PROM, passive range of motion; PRS, Physician's Rating Scale; PGA, Physicians Global Assessment Scale; PSI-SF, Parenting Stress Index-Short Form; QEK, Quantitative EMG Kinesiology;RCT, randomised control trial; ROM, Range of motion; SCALE, Selective Control Assessment of the Lower Extremity SMC, selective muscle control; SMS, Total and elastic path length- measurement of spasticity; STS, sit to stand; TS Tardieu Scale; WeeFIM, Pediatric Functional Independence Measure; VAS, visual analogue scale.

2.3.3 Methodological quality and adverse events

The methodological quality and risk of bias scoring of the studies were variable. The levels of evidence for the included studies and the quality assessment results are summarized in Table 2-4. Studies were rated according to Sackett's level of evidence I-IV (see Appendix 14.9.5), one study was identified as level I (Delgado et al., 2016b), four studies were rated as level II (Bjornson et al., 2007, Hastings-Ison et al., 2016, Kelly et al., 2019, Thomas et al., 2016)) and the remaining studies were rated level III (Schasfoort et al., 2018, Williams et al., 2013a) or IV (Löwing et al., 2017, Valentine et al., 2020b, Wright et al., 2008, Yap et al., 2010)

The quality of the studies included in the review was rated following a modified AACPDm conduct framework (see Appendix 14.9.5). Three studies (all RCTs) (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016) were rated as 'strong' methodological quality (6/7), five studies were rated as 'moderate' (4/7)(Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010) and three studies were rated as 'weak' methodological quality (3/7) (Schasfoort et al., 2018, Thomas et al., 2016, Valentine et al., 2020b).

Overall, three issues stand out as potentially raising the risk of bias for many studies in this review; firstly, failure to or being unable to determine if confounding factors were addressed, secondly a lack of information as to whether the participants were representative of the target population and thirdly incomplete data or lack of clarity on this issue.

Adequacy of power to detect statistical significance was not reported or not achieved in four studies (Löwing et al., 2017, Schasfoort et al., 2018, Williams et al., 2013a, Yap et al., 2010). Although Schasfoort et al. (2018) reported a power calculation, this was not achieved due to a breakdown in the randomisation process, and families were offered participation in the treatment group which they preferred.

Participant numbers were generally small, ranging from 15 to 65 in all studies, apart from the industry funded study by Delgado et al. (2016b), with 235 participants. In only four studies researchers were blinded to primary outcomes and unaware of the intervention status of participants (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016, Williams et al., 2013a). Detail of what constituted 'usual therapy regimens' was lacking in the majority of studies and little reference was made to the impact of co-intervention or risk of contamination for any of the studies.

Adverse Events

Only three studies reported treatment related adverse events following BoNT-A injections (Bjornson et al., 2007, Delgado et al., 2016b, Hastings-Ison et al., 2016) with none of the ninety adverse events reported classified as serious. Two studies did not present any adverse event information (Valentine et al., 2020b, Wright et al., 2008) and there were no adverse events reported in the remaining six studies.

Table 2-4 Conduct Rating Tool (AAPDM)

Study	Level/Quality	Were inclusion and exclusion criteria of the study population well described and followed?	Was the intervention well described and was there adherence to the intervention assignment? (For 2-group designs, was the control exposure also well described?)	Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?	Was the outcome assessor unaware of the intervention status of the participants (i.e., were the assessors masked)?	Did the authors conduct and report appropriate statistical evaluation including power calculations? Both need to be met to score 'yes'.	Were dropout/loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced?	Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	Score
		1	2	3	4	5	6	7	Max 7
Bjornson et al. (2007)	II/ Strong	Yes	?*	Yes	Yes	Yes	Yes	Yes	6
Delgado et al.(2016)	I/ Strong	Yes	?*	Yes	Yes	Yes	Yes	Yes	6
Hastings-Ison et al. (2016)	II/ Strong	Yes	?*	Yes	Yes	Yes	Yes	Yes	6
Kelly et al. (2019)	II/ Moderate	Yes	?*	Yes	No	Yes	?	Yes	4
Lowing et al. (2017)	IV/ Moderate	Yes	?*	Yes	No	No ¹	Yes	Yes	4
Schasfoort et al.(2018)	III/ Weak	Yes	no ²	Yes	No	No ¹ Flawed due to randomisation	Yes	No	3
Thomas et al. (2016)	II/ Weak	Yes	No ²	Yes	No	No ¥	Yes	No ²	3
Valentine et al. (2020)	IV/ Weak	Yes	No	Yes	No	No	Yes	No	3
Williams et al. (2013)	III/ Moderate	No ²	Yes	Yes	Yes	No ¹	No	Yes	4
Wright et al. (2008)	IV/ Moderate	Yes	?*	Yes	No	Yes	No	Yes	4
Yap et al. (2010)	IV/ Moderate	Yes	Yes	Yes	No	No*	No	Yes	4

¹Power calculation missing, ² Lack of detail in paper, ?*concurrent therapy detail sparse, ? not stated, ¥ statistical analysis incomplete

2.3.4 ICF Outcomes

The results for all ICF outcomes are summarised within the individual ICF domains in the sections below and have been summarised at the end of the section in Table 2-5. Further methodological details for all the studies and summaries of the main findings can be found in Appendix 14.9.6.

2.3.5 Evaluation of Body function and structure

Eighteen different outcome measures were used to evaluate change in impairment at the level of BSF following BoNT-A treatment. Results are summarised in the following sections and short term and long-term effects for BSF are summarised in Figure 2-4.

2.3.5.1 Altered Muscle Tone -Spasticity

Muscle tone was measured in eight of the eleven studies (Bjornson et al., 2007, Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Schasfoort et al., 2018, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010) with seven different measures used to evaluate spasticity and altered muscle tone. Three studies used more than one method to assess tone within their study, ranging from two (Delgado et al., 2016b, Kelly et al., 2019) to five different outcome measures (Bjornson et al., 2007).

Six out of the eight studies used the Modified Ashworth Scale (MAS) to assess spasticity (Bjornson et al., 2007, Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a, Yap et al., 2010) but the administration and scoring of the measure varied between the studies.

Three studies used the Tardieu (TS) or the Modified Tardieu Scale (MTS)(Delgado et al., 2016b, Kelly et al., 2019, Wright et al., 2008), and Schasfoort et al. (2018) used a modification of the MTS which they defined as the Angle of Catch (AOC) and recorded this as the number of degrees short of the physiological end point. Bjornson et al. (2007) also used an electromechanical method of eliciting and

measuring spasticity measuring both total and elastic path length parameters (SMS) together with two further measures of tone, deep tendon reflexes and clonus.

Short term reduction in spasticity was reported in six studies, as measured by a statistically significant change both in MAS and MTS scores ($p=.033$ to $p<.001$) with assessments ranging from four to twelve weeks post BoNT-A (Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010). However, it is of note that when a number of tone measures were used in the same study, a change in one measure of spasticity was not always reflected in a change in the other (Delgado et al., 2016b).

Delgado et al. (2016b) demonstrated a significant reduction in MAS scores in both treatment regimens compared to placebo (ABO₁₀ [10 units BoNT-A/kg] and ABO₁₅ [15 units BoNT-A/kg]) at 4 weeks and 12 weeks. However, this was only statistically significant at 4 weeks in the ABO₁₅ group when measured with MTS. Kelly et al. (2019) found significant improvement using both MAS and MTS at 4 weeks and 8 weeks, whereas Bjornson et al. (2007) failed to show any significant change in MAS or MTS following BoNT-A injections but reported significant reduction in tone as measured by deep tendon reflex and clonus at three weeks and SMS at eight weeks.

Reduction in spasticity measured over a longer time period was more variable. Löwing et al. (2017) reported improved median MAS scores from baseline at three months ($p<.001$) with a maintenance of improved MAS scores observed at 12 and 24 months. Wright et al. (2008) showed significant improvement at eight weeks but reported a 'partial' recurrence of spasticity as measured by MTS at six months in one of the two muscles injected in their study (hamstrings), with maintenance of improved spasticity observed only in the gastrocnemius muscle ($p<0.01$). Kelly et al. (2019) reported that the improvement observed in MAS and MTS at 8 weeks was no longer significant at six months.

Although studies reported change in terms of statistical significance, none of the studies related the results to minimal clinically important differences (MCID) making

it hard to draw conclusions about the clinical significance to CYPwCP of the statistically significant changes in spasticity.

2.3.5.2 Range of Motion

Range of motion (ROM) was measured in six of the eleven studies (Bjornson et al., 2007, Hastings-Ison et al., 2016, Kelly et al., 2019, Löwing et al., 2017, Schasfoort et al., 2018, Yap et al., 2010). Manual goniometry was used in all studies, except Hastings-Ison et al. (2016) who used previously validated instrumentation to measure passive ROM.

Positive short-term outcome (≤ 12 weeks) was reported in four out of the six studies (Bjornson et al., 2007, Kelly et al., 2019, Löwing et al., 2017, Yap et al., 2010). However, Schasfoort et al. (2018), found no significant change in ROM in favour of BoNT-A treatment at any time point in their study.

Those studies with a longer term follow up reported mixed results. Bjornson et al. (2007) showed significant improvement in ankle ROM at 12 weeks in favour of BoNT-A treatment but this was no longer significant at 24 weeks. Kelly et al. (2019) showed a significant improvement one week post BoNT-A treatment and a further significant improvement at 8 weeks following BoNT-A plus casting ($p < .01$) but this was no longer significant at six months.

In contrast, Löwing et al. (2017), showed a significant improvement in ROM at 3 months (mean change 6 degrees, 95% CI 4; 9, $p < .001$), which although reduced at 12 months was still significantly improved from baseline values ($p = .01$) and improvement was maintained at 24 months. Hastings-Ison et al. (2016), also showed a maintenance of improved ankle ROM when compared to baseline values over a 24-month period for both the injection frequencies in their study (four monthly and twelve monthly). The researchers suggested that maintenance of ROM over a two-year period may indicate a benefit over the expected natural history of CP (commonly associated with increasing contracture development), although in

the absence of a control group the authors acknowledge that this is difficult to prove.

Hastings-Ison et al. (2016) also identified variability in ROM changes within their subgroup analysis. They identified a difference in response between children with unilateral and bilateral involvement. Children with hemiplegia (unilateral involvement), lost a mean of 8.5 degrees of ankle range (SD 14°) over 24 months, whereas children with diplegia (bilateral involvement) increased dorsiflexion by 1.6 degrees (SD 12°) (although they found this was greater in the four monthly injection group in comparison to the 12 monthly injection group). The authors also suggested that more frequent injections may have implications for clinical practice with a potential increase in crouch gait for children with diplegia (Hastings-Ison et al., 2016, Shore Benjamin et al., 2010).

Only Yap et al. (2010) attempted to relate the change in ROM to previous injection history, suggesting that a lower number of previous injections was associated with greater change in ROM. However, with small participant numbers and a number of different multivariable models used for each outcome, their exploratory results should be interpreted with caution.

Whilst all the studies referred to statistically significant changes in ROM, none of the authors related these results to minimal clinically important differences (MCIDs).

2.3.5.3 Muscle strength and muscle selectivity

Muscle strength was measured in three studies. Williams et al. (2013a) measured strength by dynamometry and demonstrated significant isokinetic strength gains following a strengthening programme ($p=.0022$, $ES=0.57$) compared to the control period ($p=.15$, $ES =0.56$), at both 10 weeks immediately after training and at 6 months compared to baseline for all children irrespective of the timing of the training (pre or post injection). Each of the muscles targeted in the strengthening programme had significant strength improvements, including the injected

gastrocnemius and hamstring muscles. This led the authors to conclude that BoNT-A plus strengthening was superior to BoNT A alone. They also observed no significant increase in spasticity as measured by MAS over the course of the strength training ($p>.05$).

Bjornson et al. (2007) assessed strength using quantitative electromyographic kinesiology measuring maximum torque and showed significantly greater maximum torque changes from baseline ($p=.03$) at 24 weeks in favour of the BoNT-A group (but not a significant difference at 8 and 12-weeks post-injection).

Schasfoort et al. (2018) used a sit to stand test (STS) to measure functional strength and demonstrated an improvement in strength at 12 weeks, which was maintained at 24 weeks following an intensive rehabilitation programme. However, there was no statistically significant between group difference in favour of BoNT-A injections.

Two studies looked at motor control and selectivity of movement. Löwing et al. (2017) used the Selective Motor Control scale (SMC) and found that muscle selectivity improved at 3 months post injection and improvement was maintained at 24 months in comparison to baseline ($p=0.01$). Whilst Williams et al. (2013a) used the Selective Control Assessment of the Lower Extremity Scale (SCALE) and demonstrated improved motor control following BoNT-A injections [$t(13)=-2.686$, $p=.019$, $ES =0.56$] with no statistically significant difference between the two strengthening programmes (pre or post injection).

2.3.5.4 Pain, balance, muscle volume and energy cost

Pain was reported in two studies. Schasfoort et al. (2018) reported a decrease in pain at 12 and 24 weeks in the BoNT-A group and an increase in pain scores in the control group but the difference between the groups was not statistically significant. Valentine et al. (2020b) reported the presence of pain in 38.5% of the children at their final assessment but found that this was not related to other factors such as co-morbidity, BoNT-A history or participation scores and did not compare pain scores to earlier assessments.

The paediatric reach test (PRT) was used to assess functional balance in the study by Thomas et al. (2016), who reported significant within group changes for BoNT-A plus individual PT programme at 10 weeks, retained at 26 weeks ($p=.005$). However, no comparison was made with the children receiving group therapy and full statistical analysis was not provided in the text.

Change in muscle volume was measured by Williams et al. (2013a) who found a significant increase both in the control period (BoNT-A + usual care) and also following strengthening intervention (plus BoNT-A) for all muscle groups assessed, apart from the tibialis anterior muscle which only showed an increase in muscle volume following BoNT-A and strengthening ($p<.001$, $ES=.80$). There were no significant within-group differences reported for pre or post injection strength training programmes. The authors highlighted their results as potentially important in light of increasing evidence to suggest that muscle volume may reduce following BoNT-A treatment (Shortland et al., 2013).

Energy cost using the energy cost index (ECI) was evaluated in the placebo-controlled study of Bjornson et al. (2007) but no significant change was reported in either group, leading the authors to suggest that changes following BoNT-A may not be sufficient to alter gait pattern enough to affect the energy cost in CYPwCP.

In Figure 2-4, the findings regarding BSF outcomes from all the studies have been summarised and illustrated by Venn diagrams, representing those studies who have found significant and non-significant BSF outcomes following BoNT-A. This diagram highlights the timing of response and relates outcome to short term (< 6 months) and longer-term response (≥ 6 months). It also highlights the differing responses of studies which have evaluated change beyond the short term, showing the overlap between studies that have found both short- and long-term significant effects following BoNT-A and those which have only found significant changes at one time point.

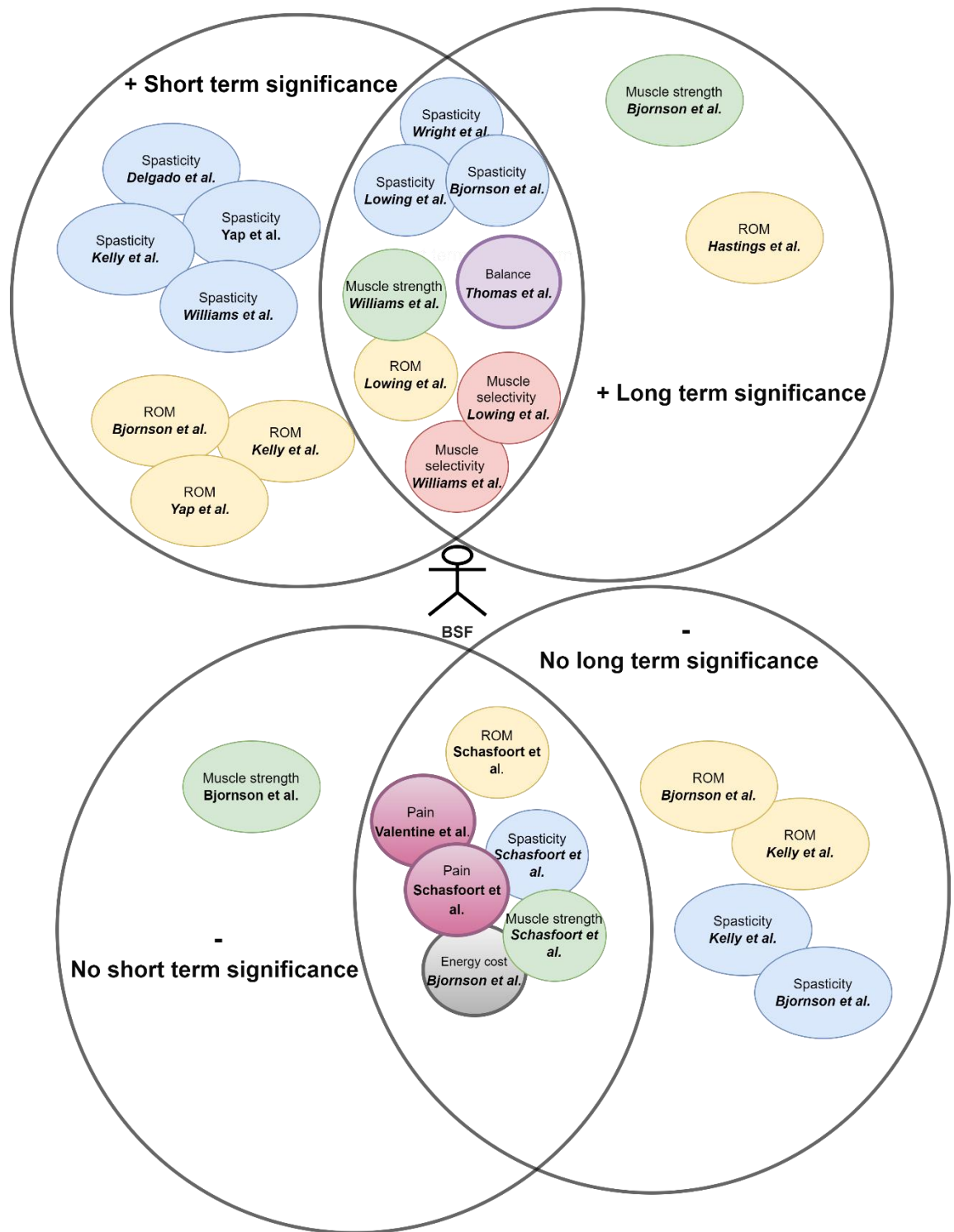


Figure 2-4 Summary of short-term and long-term significant changes in the BSF domain following BoNT-A

Key: ROM= Joint Range of Motion, short-term significance < 6 months, long-term significance ≥ 6 months.

2.3.6 Evaluation of activity

Fifteen different outcome measures were used to evaluate a change in activity following BoNT-A treatment. The activity changes reported are detailed below, short- and long-term results summarised in Figure 2-5.

2.3.6.1 Gross motor function

The Gross Motor Function Measure (GMFM) was the most frequently used measure to assess gross motor function. Both GMFM versions were used, GMFM -88 and GMFM-66, and GMFM results reported in six studies (Bjornson et al., 2007, Kelly et al., 2019, Thomas et al., 2016, Valentine et al., 2020b, Wright et al., 2008, Yap et al., 2010). Significantly improved change scores from baseline were reported in all studies apart from Thomas et al. (2016), who reported no significant change following BoNT -A plus PT (for either individual or group sessions) over a 6 month period. Valentine et al. (2020b), reported no loss of motor function in their GMFCS Level II cohort following long term BoNT-A use as related to published GMFM scores (Rosenbaum et al., 2002). The authors suggested this was a maintenance of motor function but in the absence of baseline GMFM scores this makes evaluation difficult.

Significant short term (≤ 12 weeks) improvements in GMFM scores were shown in three studies following BoNT-A treatment (Kelly et al., 2019, Wright et al., 2008, Yap et al., 2010). Longer term results were reported by Wright et al. (2008) who showed further improvement at six months ($p < .001$), as did Kelly et al. (2019), who reported a significant improvement at six months ($p = .002$) with trends of increasing GMFM scores from baseline to 6 months for both casting protocols following BoNT-A. Bjornson et al. (2007), although reporting improvement at all time points from baseline only found this to be statistically significant at 6 months ($p < .001$) in favour of BoNT-A treatment compared to placebo.

Only Yap et al. (2010) related a change in gross motor function to other variables and found that improved scores were observed with younger age ($r = 0.43, p = 0.015$) and fewer previous injections ($r = 0.40, p = 0.024$).

2.3.6.2 Gait

Gait changes were assessed by twelve different outcome measures in eight of the eleven studies (Delgado et al., 2016b, Hastings-Ison et al., 2016, Kelly et al., 2019, Löwing et al., 2017, Schasfoort et al., 2018, Thomas et al., 2016, Wright et al., 2008, Yap et al., 2010) with varying degrees of response reported following BoNT-A treatment.

Significant improvement in favour of BoNT-A treatment was reported in six of the eight studies. Delgado et al. (2016b) used the Physician's Global Assessment (PGA) outcome measure to evaluate gait changes and showed significant improvement ($p < .001$) in favour of both ABO treatment groups at 4 weeks (ABO₁₅ 1.54 [95%CI 1.28,1.81]; ABO₁₀ 1.50[1.283,1.77]) in comparison to placebo (0.73 [0.46,0.99]). This significant difference was maintained at 12 weeks. Yap et al. (2010) demonstrated gait improvement from baseline using the modified Physician Rating Scale (mPRS) at 12 weeks ($p < .001$). Wright et al. (2008) demonstrated gait improvement with significantly improved scores from baseline using a timed walk test at 8 weeks, which was also maintained at six months ($p < .05$) but no confidence intervals were provided.

Löwing et al. (2017) used 3-Dimensional Gait Analysis (3DGA) and reported a statistically significant change of 4.1 points in the Gait deviation index at 12 months (95% CI 0.7;7.5, $p = 0.02$) following BONT-A injections, however in the absence of published MCIDs, the authors were unsure of the clinical significance of this result.

Hastings-Ison et al. (2016) also used 3DGA to measure ankle dorsiflexion in the stance phase of gait, in excess of the Minimum Detectable Change (MDC $> 5^\circ$), which they classified as a measure of 'motor responsiveness' following the final BoNT-A injection within their 24-month study. Although they reported improvement and no significant between group differences for their injection frequencies ($p = .19$), statistical information was lacking about the significance of change from baseline for the total sample, making it difficult to evaluate the significance of this change. Schasfoort et al. (2018) demonstrated minimal changes in kinematic gait

parameters in favour of the BoNT-A treatment in only one of the 8 gait parameters evaluated 'reduced knee flexion in swing' - at 24 weeks (-5.6 °[95% CI-10.8,-0.4]p=.034) using 2-Dimensional Gait Analysis (2DGA) but found no significant difference in favour of BoNT-A in other gait outcomes. This led the authors to conclude that BoNT-A plus intensive rehabilitation did not significantly improve gait.

The level of ambulation was also used as a proxy gait measure. This was measured by the Functional Assessment Questionnaire (FAQ) by Yap et al. (2010), who found significant improvement in score at 12 weeks following casting and BoNT-A in comparison to baseline scores (p=.005). This contrasted with the findings of Hastings-Ison et al. (2016) who found a non-significant improvement in median FAQ scores following BoNT-A. The same group also used the Functional Mobility Scale (FMS) to evaluate change in level of ambulation following BoNT-A and although they demonstrated an improvement in FMS 500 m walk from baseline to 26 months for both groups (four monthly and twelve-monthly injections) with no significant between group difference, the significance of the change from baseline was not reported (Hastings-Ison et al., 2016).

In contrast, no significant changes were found in any of the gait parameters measured by Gaitrite™ (Kelly et al., 2019), or Edinburgh Visual Gait Scale (EVGS) (Thomas et al., 2016) and 1-minute fast walk test (Thomas et al., 2016) following BoNT-A treatment.

In Figure 2-5, the findings regarding Activity outcomes from all of the studies have been summarised and illustrated by Venn diagrams, representing those studies which have found significant (and non-significant) Activity outcomes following BoNT-A. This diagram highlights the timing of response and relates outcome to short term (≤ 6 months) and longer-term response (> 6 months). It also highlights the differing responses of studies which have evaluated change beyond the short term, showing the overlap between studies that have found both short- and longer-term significant effects following BoNT-A and those which have only found significant changes at one time point.

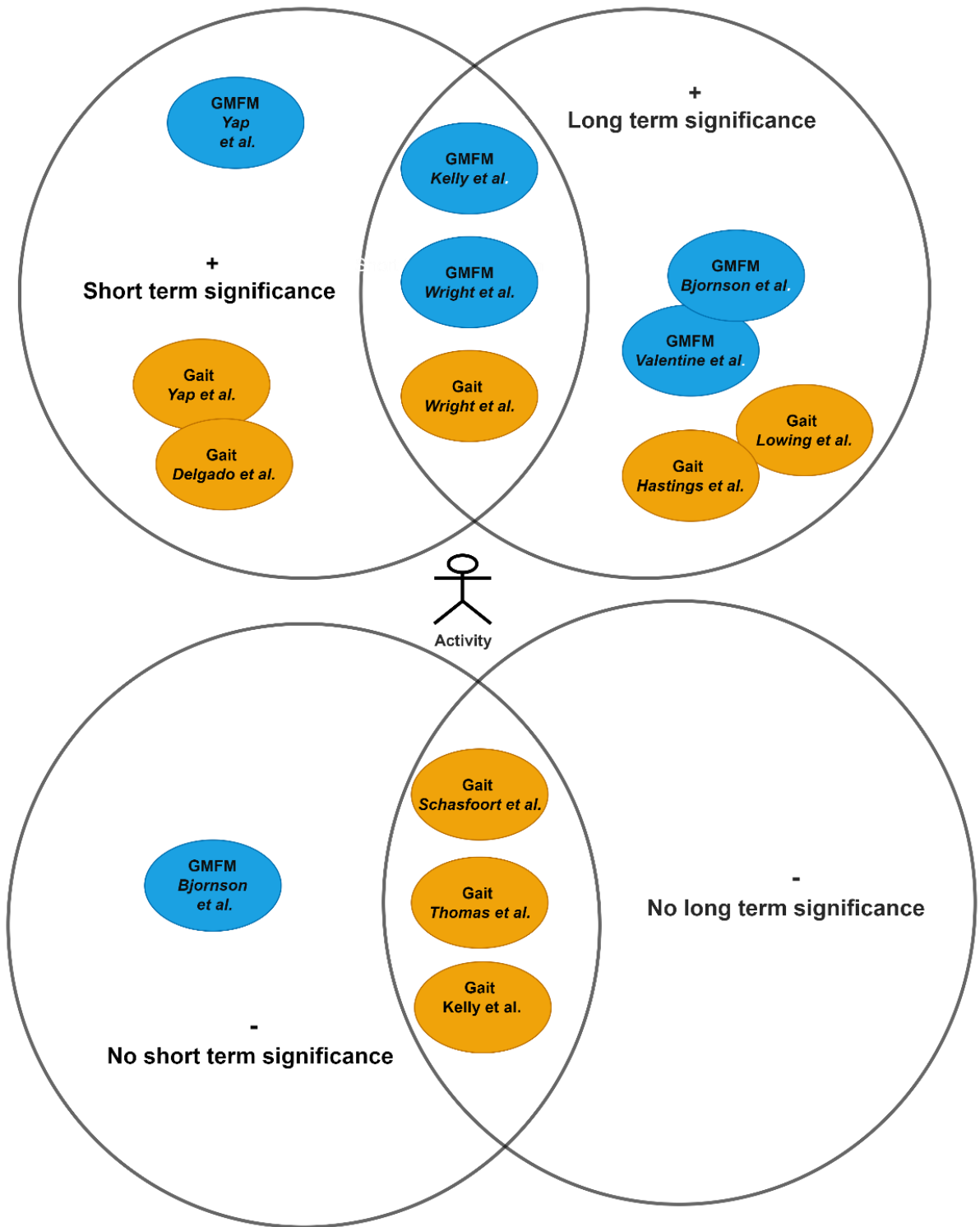


Figure 2-5 Summary of short-term and long-term significant changes in Activity domain following BoNT-A

Key: GMFM=Gross Motor Function Measure, short-term significance < 6 months, long-term significance ≥ 6 months.

2.3.7 Evaluation of participation

Participation was measured by ten outcome measures in the 11 studies. The Participation and Health related Quality of Life (HRQoL) results are described below, summarised in Figure 2-6.

The Goal attainment Scale (GAS) was used to measure change in activity and participation in five of the eleven studies (Bjornson et al., 2007, Delgado et al., 2016b, Löwing et al., 2017, Schasfoort et al., 2018). Short term significant improvement in GAS scores were shown in three studies at initial assessment time points (Delgado et al., 2016b, Löwing et al., 2017, Williams et al., 2013a) (between 4 and 12 weeks post BoNT-A treatment) and this improvement was maintained in the two longer term studies at 6 months (Williams et al., 2013a) and 24 months (Löwing et al., 2017). The two remaining studies noted an improvement in GAS scores over a 6-month period but reported no significant difference in favour of BoNT-A group at any time point either at three or six month follow up (Bjornson et al., 2007, Schasfoort et al., 2018).

The Canadian Occupational Performance Measure (COPM) was used in 2 studies (Bjornson et al., 2007, Thomas et al., 2016). Bjornson et al. (2007), observed a significant improvement ($p=.04$) in COPM Performance scores in favour of BoNT -A at 12 weeks (mean change score 1.7 (SD 1.4) versus 1.2 (SD 1.7)) in the control group and whilst this remained clinically significant at six months (change score ≥ 2) this was no longer statistically significant in favour of BoNT-A intervention. COPM Satisfaction scores were not significantly improved from baseline at any time point. Thomas et al. (2016), found improved COPM scores following BoNT-A which were statistically and clinically significant for both individual and group physiotherapy at 10 weeks ($p<.001$) and these remained statistically significant at 26 weeks.

The Pediatric Evaluation of Disability Inventory (PEDI) was used in two studies. Kelly et al. (2019), noted a significant improvement in all PEDI domains (except social function caregiver assistance) at 2 months and six months in comparison to baseline ($p=.009$ to $<.001$) with no significant difference between the two casting groups.

The significant improvement in scores for both groups at 6 months exceeded the minimal clinically important difference (MCID) of 11% in three of the six domains in the single cast group (self-care, social function, and self-care with caregiver assistance) and in the serial cast group (mobility, social function, and self-care with caregiver assistance).

A significant improvement in PEDI scores was also found by Wright et al. (2008), who observed statistically significant changes in all PEDI domains (except self-care) at eight weeks, which significantly improved further in all domains at six months following BoNT-A injections ($p < .001$ to $< .0001$). The same group also found statistically significant improvement in the Pediatric Outcomes Data Collection instrument (PODCI) global score at 8 weeks ($p < .01$) and at six months ($p < .001$) in the same study (Wright et al., 2008).

The Pediatric Functional Independence Measure (WeeFim) was used in one study to evaluate participation and functional independence but there was no significant change in scores following BoNT-A at 12 weeks (Yap et al., 2010). Valentine et al. (2020b), used the Participation and Environment Measure-Child and Youth (PEM-CY) to evaluate participation, reporting cross sectional median scores for a subsection of PEM-CY measuring a child's 'involvement' in participation at home, school, and community. The results were provided in isolation at a single time point with the absence of reference values making interpretation of individual scores difficult. They also found no significant relationship between PEM-CY scores and topography, GMFCS level, pain or BMI but did find a negative correlation between GMFM score and PEM-CY school participation scores. The authors postulated that children who were more able but were still far from their peers' motor ability tended to feel isolated and left out of motor-based activities at school.

2.3.8 Health Related Quality of Life

Two measures were used to evaluate health related quality of life (HRQoL). The Cerebral Palsy Quality of Life Measure (CPQOL) and the Child Health Questionnaire (CHQ).

CPQOL was used in two studies (Kelly et al., 2019, Thomas et al., 2016) to evaluate change following BoNT-A plus two casting protocols and two methods of Physiotherapy delivery. Kelly et al. (2019) reported no significant improvement in CPQOL scores. However, Thomas et al. (2016) found a significant improvement in scores which favoured group therapy following BoNT-A at 10 weeks for the 'access to services' domain but this was no longer significant at six months and there were no between-group differences in the other four domains at any time point. Lack of detail regarding full statistical analysis of CPQOL scores makes further evaluation of their results difficult.

The Child Health Questionnaire (CHQ) was used by Hastings-Ison et al. (2016) to evaluate HRQoL following two BoNT-A injection frequencies, four-monthly and yearly. They found no significant between-group differences for any of the thirteen domains, however no detail was provided regarding the change in CHQ for both groups following BoNT-A.

Other determinants of responsiveness to BoNT-A considered parenting stress measured using the Parenting Stress Index -Short Form (PSI-SF) and child motivation assessed by parental report using the Dimensions of Mastery Questionnaire (DMQ). Significant associations were reported in the study by Yap et al. (2010), between all the outcomes studied and elements of the DMQ and PSI-SF. On multivariable analysis, low social persistence (child's motivation to be with their peers) and low levels of parental stress were associated with greater change in tone ($p=.006-.017$ respectively). In children who were highly motivated there was also a statistically significant but moderate strength correlation with a change in gait pattern ($r=0.39$, $p=0.023$) and ROM ($r=-0.41$, $p=0.008$). The study concluded that parenting stress could either positively or negatively influence the change in a child's level of ambulation. However, without a comparison group the authors suggested it was difficult to attribute changes to BoNT-A treatment and the authors urged caution in the generalisability of their results due to the number of multivariable models tested and the small sample size (31 children).

In Figure 2-6 once again the findings regarding Participation and QoL outcomes from all the studies have been summarised and illustrated by Venn diagrams, representing those studies who have found significant and non-significant outcome following BoNT-A. This diagram highlights the timing of response and relates outcome to short term (< 6 months) and longer-term response (\geq 6 months). It also shows the overlap between studies that have found both short- and long-term significant effects following BoNT-A and those which have only found significant changes at one time point.

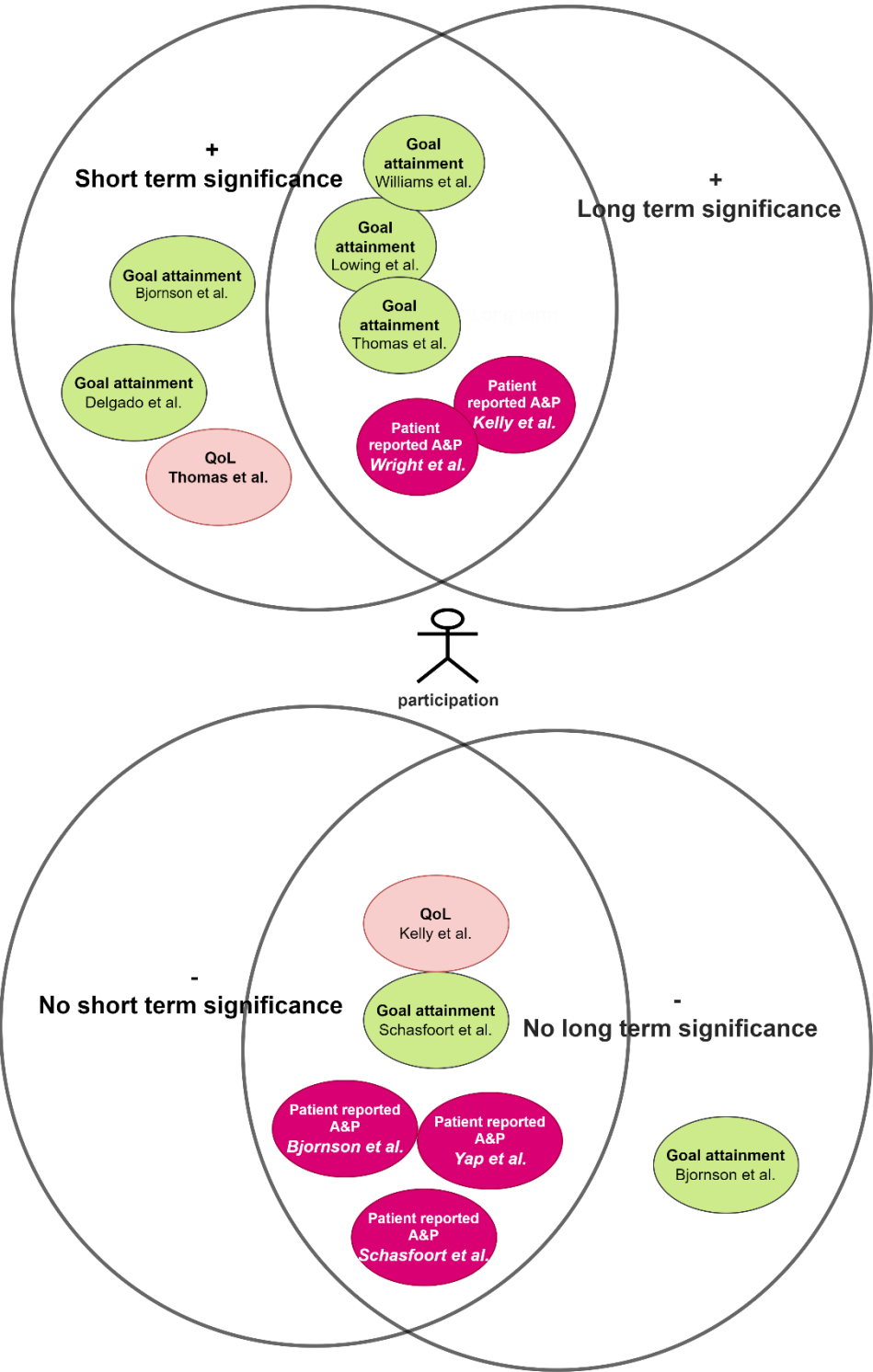


Figure 2-6 Summary of short-term and long-term significant changes in the Participation domain following BoNT-A

Key: A&P=Activity and Participation measures / QoL= Health related Quality of Life measures
 short-term significance < 6 months, long-term significance ≥ 6 months.

2.3.9 Integration of the findings between the ICF domains

Although all studies reported outcomes in the three domains of the ICF body function and structure, activity, and participation, not all investigated the relationship between change in outcomes between the different ICF domains.

Two studies (Löwing et al., 2017, Wright et al., 2008) attempted to investigate the association between a change in biomedical impairment measured through outcomes in body function and structure domain of the ICF following BoNT-A treatment and the functional outcome of these changes in terms of outcomes in activity and participation domains of the ICF.

Löwing et al. (2017), identified improvement in spasticity after three months following BoNT-A treatment which remained stable over 24 months, together with a significant (but clinically small) long term improvement in gait. Goal attainment also increased significantly at three months and twelve months and was maintained at 24 months. However, they were unable to correlate spasticity reduction with an improvement in gait or goal attainment.

Similarly, Wright et al. (2008), reported significant improvement in body function and structure outcomes (including reduced spasticity) together with improvements in activity and participation at two months post BoNT-A treatment. They observed continued improvement in activity and participation domains at six months despite a partial recurrence of spasticity. However, despite moderate to strong correlation for the different ICF domains at baseline, the strength of change score relationship was typically no more than fair. Body function and structure outcomes (reflecting spasticity scores) accounted for less than 50% of the explained variation in activity and participation change score models

Other studies attempted to explain their results by exploring links between results in the ICF domains. Bjornson et al. (2007), found that changes in BSF outcome measures following BoNT-A were associated with improved gross motor function at six months but did not find a significant improvement in family satisfaction. Kelly et

al. (2019), demonstrated short term reduction in spasticity at 8 weeks which was associated with improved function and activity outcomes at six months (but not significant gait changes), but reported that this did not improve quality of life outcomes.

Yap et al. (2010), attempted to identify intrinsic and extrinsic factors associated with BoNT-A treatment and suggested that for their group of mainly GMFCS Level I children, age, number of treatments, parental stress and child motivation appeared to influence the degree of responsiveness to BoNT-A treatment. However, the authors urge caution regarding the generalisability of their results in view of the small sample size and number of multivariable models tested for each outcome to find the best predictive models.

A summary of the results from the included studies for all ICF domains are shown in Table 2-5.

Table 2-5 Systematic Review Results by ICF Domains showing short-term and long-term statistical significance of outcomes following BoNT-A

ICF	Outcome	Bjornson et al. (2007)		Delgado et al. (2016)		Hastings-Ison et al. (2016)		Kelly et al. (2019)		Lowing et al. (2017)		Schasfoort et al. (2018)		Thomas et al. (2016)		Valentine et al. (2020)		Williams et al. (2013)		Wright et al. (2008)		Yap et al. (2010)		
		ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	
BSF	Spasticity	Green	Red	Green				Green	Green	Green	Green	Red	Red					Green	Green	Green	Green	Green		
	ROM	Green	Red				Green	Green	Green	Green	Green	Red	Red										Green	
	Muscle strength	Red	Green							Green	Green	Red	Red						Green	Green				
	Muscle selectivity																		Green	Green				
	Pain												Red	Red						Yellow				
	Energy cost/balance	Red	Red												Red	Red								
ACTIVITY	Gait			Green			Green	Red	Red		Green	Red	Red	Red	Red						Green	Green	Green	
	GMFM	Red	Green					Green	Green					Red	Red			Green			Green	Green	Green	
PARTICIPATION	Goal Attainment	Green	Red	Green						Green	Green	Red	Red	Green	Green				Green	Green				
	Patient Reported Activity & Participation	Red	Red			Yellow	Yellow	Green	Green			Red	Red				Yellow				Green	Green	Red	
	QoL					Yellow	Yellow	Red	Red					Green	Green									

KEY: Red No significant difference in favour of BoNT-A / Green Significant difference in favour of BoNT-A / Yellow Unclear ST=short term < 6 months LT=Long term ≥ 6 months

2.4 Discussion

The primary aim of this systematic review was to summarise the evidence of effectiveness of lower limb BoNT-A treatment in ambulant children with CP, as evaluated by outcomes measured within the three ICF domains of body structure and function, activity, and participation.

Applying the inclusion criteria to the results of the searches identified eleven empirical papers that included outcomes in all three of the ICF domains for inclusion in this review. This is fewer than anticipated, and surprising when one considers that the ICF was introduced over two decades ago, with the paediatric model (ICF-CY) launched fifteen years ago. Since that time there has been a plethora of editorials and national guidelines advocating the adoption of the ICF framework to evaluate treatment interventions in CP as meaningful for CYPwCP and their families (Mugglestone et al., 2012, Rosenbaum and Gorter, 2012, Rosenbaum and Stewart, 2004).

Clinicians and researchers have been encouraged to adopt a family-centred approach and focus on areas that are considered meaningful to children and their families when evaluating the efficacy of treatment interventions (Palisano et al., 2017). This requires clinicians and researchers to evaluate the benefits of treatment by including outcome measures in ICF domains which go beyond the level of body structures and function outcomes (Annette, 2006, Rosenbaum, 2020). The lack of research including outcomes in all three domains of the ICF is therefore particularly pertinent, as young people with CP and their families have frequently identified treatment priorities relating to activity and participation (Palisano et al., 2017, Roebroek et al., 2009).

2.4.1 Quality of evidence

The level of evidence (Sackett, 1997) within the studies included in the review was varied, with less than half of the papers classified as level I or II studies, and the remainder classified as Level III or IV. The number of level III and IV studies was not

unexpected and is in keeping with the majority of research within the field of neurodisability, where a variety of research designs are employed (WIART et al., 2012). The quality of the included studies was mixed. As only two of the studies had a placebo control group (Bjornson et al., 2007, Delgado et al., 2016b) the assumptions from the remaining nine studies may need to be interpreted with caution as to the direct effect of BoNT-A injections on change in outcome for CYPwCP.

As expected multiple outcomes were assessed throughout the ICF domains in this review. Several studies assessed a number of outcomes within each ICF domain (such as spasticity) without specifying a single primary outcome. Assessing outcome throughout the whole ICF is encouraged if meaningful change is to be evaluated. However, there can be limitations in assessing multiple outcomes, particularly in studies with small sample sizes (Kelly et al., 2019, Williams et al., 2013a) when multiple comparisons may well result in type I errors.

2.4.2 Review findings within the ICF domains – short term versus long term change

Outcomes within the ICF domains were reported as short-term change (less than six months) and long-term change (greater than six months) relative to baseline scores. A summary of the results for all the studies can be found in Table 2-5 (see Appendix 14.9.6 for detailed summary).

Short-term changes were shown throughout all of the domains of the ICF following BoNT-A treatment. Most studies were able to demonstrate a short term improvement in body structure and function outcomes, particularly a reduction in spasticity (Bjornson et al., 2007, Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010) and improved range of motion (Bjornson et al., 2007, Kelly et al., 2019, Löwing et al., 2017, Yap et al., 2010). In some cases this appeared to be associated with a short-term improvement in the activity and participation domains with improved gross motor function (Wright et al., 2008, Yap et al., 2010) and gait (Delgado et al., 2016b,

Löwing et al., 2017, Wright et al., 2008, Yap et al., 2010), as well as increased participation outcomes (Bjornson et al., 2007, Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Thomas et al., 2016, Williams et al., 2013a, Wright et al., 2008).

The results from studies reporting longer-term effects (six-months to two years) were variable. As expected, there was little evidence of a sustained change in body function and structure outcomes beyond six months. Few studies described long term reduction in spasticity (Löwing et al., 2017, Wright et al., 2008) or long-term improvement in ROM (Hastings-Ison et al., 2016, Löwing et al., 2017). In some studies improvement in gross motor function was shown after 6 months (Bjornson et al., 2007, Kelly et al., 2019, Wright et al., 2008), however, there were fewer long term changes in gait parameters reported in any of the studies (Hastings-Ison et al., 2016, Löwing et al., 2017, Wright et al., 2008). In many cases it was difficult to relate change in activity and participation directly with the intervention of BoNT-A treatment alone.

Despite the variability shown when describing the effect of BoNT-A injections beyond six months, three studies considered a lack of deterioration in body function and structure and activity outcomes to be a positive outcome. They suggested maintenance of ROM could be interpreted as a potential benefit over the expected natural history of potential deterioration in these outcomes with growth in CYPwCP (Hastings-Ison et al., 2016, Löwing et al., 2017, Valentine et al., 2020b).

There was some evidence to suggest that a more prolonged change occurs following BoNT-A treatment at the participation level as measured by GAS, COPM-P and PEDI. Improvement in participation outcomes appeared to be maintained beyond six months, despite a gradual return towards baseline in BSF outcome measures (Löwing et al., 2017, Thomas et al., 2016, Williams et al., 2013a, Wright et al., 2008). There was less evidence to suggest that any changes resulted in any significant change in health related quality of life (Hastings-Ison et al., 2016, Kelly et

al., 2019, Thomas et al., 2016) or parental satisfaction as measured by COPM-S (Bjornson et al., 2007).

These findings of improved short-term outcomes in the BSF domain agree with other published literature (Blumetti et al., 2019, Kahraman et al., 2016, Ryll et al., 2011b). Of note however, was the evidence of improvement beyond six months in outcomes in the activity and participation domains despite a return towards baseline of outcomes in the body structure and function domains.

2.4.3 Relating change between ICF domains

Although several studies attempted to relate change throughout the three ICF domains following BoNT-A treatment (Bjornson et al., 2007, Kelly et al., 2019, Löwing et al., 2017, Wright et al., 2008), there appeared to be a lack of correlation between the various outcome measures used throughout the ICF in association with baseline scores. Despite moderate to strong relationships between body structure and function measures and both activity and participation measures at baseline, the strength of change score relationships following BoNT-A injections were typically no more than fair (Löwing et al., 2017, Wright et al., 2008).

These findings support the emerging theory that the relationship between ICF domains is not linear and changes in impairment as measured by body structure and function outcomes do not always translate into improvement in the other domains of the ICF (Rosenbaum, 2020).

There are a number of difficulties when attempting to evaluate treatment effects in this population. Firstly, there is the effect of maturation on a child's changing motor ability as part of the natural history of CP. Secondly, in early childhood motor development is usually rapid, and the effects of many of the interventions used in CP, including BoNT-A, can be comparatively slow. Thirdly many other therapeutic interventions may be carried out concurrently with BoNT-A injections, which are not standardised between individual CYPwCP.

Against this background of multifaceted changes, influenced by both growth and development, it can be difficult to detect causal connections between interventions and outcomes that can be totally attributed to the treatment received. This issue can be further compounded by the description of rehabilitation interventions as 'usual care' in terms of the physiotherapy provided in some of the studies. This lack of transparency is often referred to as the '*black box of therapy*' and creates obstacles to evaluating which elements of the intervention are most important (Jette, 2020). The use of generic terms such as 'usual care', without giving details of what constitutes usual care, including dosage and content, can make replication of interventional studies difficult. None of the eleven papers in this review gave a detailed account of co-intervention or treatment fidelity.

Relationships between changes at different ICF levels are complex and multifaceted with any gains in activity and participation post BoNT-A likely to be influenced by contextual child and environment factors. Child, family, and treatment characteristics can all influence the degree of responsiveness to BoNT-A treatment. Only one study attempted to evaluate the contribution of contextual factors to the efficacy of BoNT-A treatment and casting (Yap et al., 2010). Contextual factors (including environmental and personal factors) are probably underappreciated in this population, particularly when factors such as child motivation and parental stress may potentially be modifiable and should be considered alongside the interventions for ambulant children with CP.

2.4.4 Outcome measures used in evaluating BoNT-A use in ambulant CYPwCP

An important target of treatment in the CP population is increased participation, with enhanced participation often regarded as the ultimate goal of treatment (Imms et al., 2017). Although there is increasing recognition of the importance of measuring the effects of interventions on improving participation in children with CP, the use of validated outcome measures to measure participation in both research and clinical practice is often lacking (Sakzewski et al., 2007). This was confirmed when reviewing studies for inclusion in this review, as highlighted earlier,

46% of the full papers included for initial screening were rejected because they lacked such a measure.

Many of the participation measures used in this review (including PEDI, PODCI, WeeFIM) incorporate an element of measuring activity and participation together (Rozkalne and Bertule, 2014). Whilst GAS and COPM are accepted measures to evaluate change in participation goals, there is a lack of detail in the majority of the studies about what specific treatment goals are, making comparison between the studies difficult. Within this review only Delgado et al. (2016b), gave detail regarding the goals set. Although others alluded to the types of goals set during their discussion (Löwing et al., 2017, Wright et al., 2008), the remaining papers did not provide any further detail which makes both comparison and replication of studies difficult.

Another pertinent issue to consider is how closely the goals set align with both the child's and parents' desire for change following BoNT-A treatment. In the study by Delgado et al. (2016b), parents were asked to choose from a list of preselected goals specifically defined for their study. The use of predetermined sets of goals may restrict families from choosing goals that are most meaningful to their child. There has been ongoing difficulty demonstrating the efficacy of BoNT-A treatment to improve function and participation goals (Blumetti et al., 2019) and it has been suggested that a series of individualised goals may be more meaningful to families rather than using generic pre-set goals (Damiano, 2014).

In addition to the wide range of unspecified goals set within the studies, there is also the need to consider the wider notion of participation, and consider what has recently been described as the 'concept of participation related constructs' (Imms et al., 2017). This concept recognises that participation has two essential components; attendance, which can be described in terms of frequency of attendance or the range of activities a child does; and involvement, which refers to the child's experience of, and their degree of participation in, an activity. Within this review only Valentine et al. (2020b), measured participation status in terms of

a child's average involvement in participation activities. The addition of recording a child's average involvement in participation activities was novel but unfortunately the significance of the results was hard to interpret in the absence of baseline participation data.

The extensive variety of outcome measures used within studies describing BoNT-A efficacy greatly limits the ability to make comparisons between studies. It is difficult to pool data, in what are essentially small, often underpowered studies, in order to make clinically relevant, evidence-based recommendations. In this review alone there were 43 different outcome measures used throughout the 11 studies (see Figure 2-3). Even when the same outcome measures were used, variation in the administration and lack of clarity about scoring of the measures impeded clear interpretation of statistically significant results.

The ability to detect minimal clinically significant change is also a vital consideration in the measurement of outcomes in clinical research (Morris et al., 2005, Weaver et al., 2020). It was often difficult to interpret meaningful change within the studies in this review, as although the results were often described as statistically significant, the majority of the studies failed to relate changes to minimal clinically important differences (MCIDs). This is described as the smallest difference in outcome which is perceived to be beneficial to the CYPwCP, or minimum detectable changes (MDCs), the degree of improvement beyond measurement error. Therefore, in many cases, it is difficult to determine the true clinical benefit of the intervention for CYPwCP. This was alluded to in the study by Lowing et al. (Löwing et al., 2017), who observed that despite statistically significant changes observed in standardised outcomes throughout the ICF, the magnitude of change was not sufficient to result in a meaningful change to the child or their family as rated by patient related outcome measures.

Others questioned the sensitivity of HRQoL measures to detect meaningful change following BoNT-A intervention, especially in the absence of published MCIDs (Bjornson et al., 2007, Kelly et al., 2019). There may also be a mismatch between

change reported by families and the standardised outcome measures used, with parents frequently describing changes in movement quality which are not objectively measured in standardised testing, especially in the BSF and activity domains (Wright et al., 2008). There has also been some discussion regarding the appropriateness of outcome measures in the BSF and Activity domains which only measure a child's 'capacity' i.e. what they can do in standardised testing and not the child's true 'performance' i.e. what they do in everyday life (Burgess et al., 2021).

What is markedly absent in all of the papers reviewed is the voice of the child with CP and their family. Even in the studies where mixed methodology has been used, the qualitative findings were not reported alongside the quantitative data from the ICF domains, and no attempt was made to integrate the two.

2.4.5 Variation within the review- population, previous treatment history and length of follow up

The CP population is acknowledged to be extremely heterogeneous (MacLennan et al., 2015), with a marked difference in functional ability both between and within different GMFCS levels (Reid et al., 2011). Moreover, this is further complicated by non-motor components such as sensory disturbances and differing cognitive capacity (Graham et al., 2016). It is increasingly recognised that although children within GMFCS levels I to III are all classified as ambulant, those children in GMFCS levels I and II are more frequently considered as a separate group with the ability to walk independently (without aids). This makes comparison between GMFCS levels I-III difficult in the published studies. Indeed, in the 11 studies in this review only 9% of the 938 children studied were classified as GMFCS level III. Only two studies (Schasfoort et al., 2018, Wright et al., 2008), reported results from balanced groups of children at GMFCS levels I, II and III. This obviously raises questions as to how applicable these results are to children in GMFCS level III.

Within this review, there was a lack of consensus in reporting changes in outcome related to age, topography, GMFCS level and number of previous injection sessions in the 11 studies reviewed. There was a significant variety in the number of

previous injections children had received and no attempt was made by any of the studies, apart from Yap et al. (2010) to relate outcome to a child's age or number of previous injections.

Although some studies reported change in BSF outcomes as early as 4 weeks post BoNT-A (Delgado et al., 2016b), most studies had a moderate follow up time of six months, with only two studies following children up for 24 months (Hastings-Ison et al., 2016, Löwing et al., 2017). The duration of follow up is likely to be an increasingly important consideration given the mounting evidence that repeated use of BoNT-A may be harmful to children with ambulant CP (Gough, 2009, Multani et al., 2019a, Multani et al., 2019b).

Concerns have been expressed regarding harmful changes at the muscle level following the use of repeated injections and potential deterioration in function leading to limitation in participation opportunities (Hastings-Ison et al., 2016). Other researchers have disagreed and suggest there is little evidence to show deterioration in the muscle, reduced motor function or participation with repeated BoNT-A injections (Löwing et al., 2017, Valentine et al., 2020b, Williams et al., 2013a). More research into repeated injection cycles and longer follow up times reflecting pragmatic varied clinical practice should address these conflicting arguments.

2.5 Strengths and Limitations

2.5.1 Strengths

The piloting of the search strategy and supplementation of the results of the electronic search with hand searching (including further review of reference lists of systematic reviews and included papers), allows confidence that all relevant English language research at the time of the final search was included in this systematic review. The conclusions arising from it are believed to be based on all the available current evidence.

2.5.2 Limitations

The main limitation of this review relates to the available evidence on the subject. As illustrated in the methodology, from the 82 studies selected from the initial title and abstract screening only 11 could be included as fulfilling selection criteria.

CP although classified as a singular healthcare condition, is such a heterogeneous condition, that the benefits of interventions such as BoNT-A (which could benefit an individual with CP) are difficult to investigate with rigorous research methods. Within the 11 studies included there was wide variability in participant selection, methodology, outcome measures and follow up time, which, as in much CP research, makes it difficult to compare outcomes between the studies and draw clear conclusions.

The lack of a control group in nine of the eleven studies is not unusual when evaluating an established treatment modality such as BoNT-A. It is acknowledged that a control group can be unfeasible for many practical and ethical reasons. Nevertheless, a lack of control group together with the relatively low level of evidence of these studies does restrict causal inferences about the benefits of BoNT-A treatment. Within these studies it can be difficult to isolate the causal effect of BoNT-A from the many sources of bias and threats to validity including concurrent events such as co-intervention of other therapy.

When considering the evaluation of established treatments such as BoNT-A in clinical practice, it is important to recognise the benefits of different study designs for addressing pragmatic research questions. Within paediatric rehabilitation medicine the best research design may not always be the use of randomised controlled trial. Mixed methods research designs, 'can be very powerful and considered by many to be essential' (Rosenbaum, 2020). Interventions rarely exist in isolation for the child with CP and are often part of a multifaceted rehabilitation programmes with many outcomes of interest. It is important to consider whether the best measures available are being used to assess the impact of interventions

There are some limitations to the generalizability of the results in this review to CYPwCP in GMFCS Level III due to the small numbers of GMFCS Level III children included in the studies reviewed.

The review highlights important unanswered questions particularly in relation to evaluating the impact of BoNT-A on activity and participation domains which will enable more objective study planning in the future. It also demonstrates the absence of important MCIDs to enable the assessment of the true meaningful effect on CYPwCP of BoNT-A intervention.

2.6 Conclusion and recommendations for future research

Research evaluating interventions for CYPwCP is challenging. This review has highlighted a number of limitations with existing studies looking at change across the ICF domains. These included small sample sizes, heterogeneous patient groups, short follow up time and varied outcome measures with few details of how the studies were conducted to allow replication. The use of BoNT-A in CYPwCP needs further evaluation. Whilst BoNT-A use in the domain of body structure and function appears to be well established, further investigation of the efficacy of treatment should focus on clinically important outcomes in both activity and participation domains using standardised clinical measures for evaluation.

As this review has indicated, there is a need to increase the evidence base with more high-quality studies which include outcomes within all the domains of the ICF. Doing so will enable the development of a common narrative regarding meaningful outcomes evaluating the efficacy of BoNT-A use. Identifying and measuring these outcomes and the factors that influence them will ultimately enable clinicians to target BoNT-A treatment to children who are most likely to benefit from the treatment. Furthermore, with increased high quality research in this area, a consensus could be reached on a core set of outcome measures required in each domain of the ICF. These would need to be validated and meaningful to children and their families. If such measures were used and detailed information about co-

intervention criteria reported, studies with this population following BoNT-A treatment could be compared and robust conclusions drawn.

2.6.1 Future Research

There is a need for pragmatic clinical studies which can evaluate the complex clinical practice that occurs when CYPwCP receive BoNT-A treatment. It is essential to look at outcomes across all ICF domains, not only evaluating impairments of body structure and function which are directly affected by BoNT-A treatment, but also the evaluation of activity limitation and participation restriction that are indirectly affected. Most importantly there is a need to assess the clinical benefits in terms of meaningful change to children receiving treatment. This will allow clinicians and families to target interventions to promote improved functioning and participation and wellbeing.

The selection of standardised outcome measures throughout the ICF which are sensitive to change following BoNT-A treatment will contribute to the evidence base regarding the efficacy of BoNT-A use in CP. Establishing the most useful outcome measures in the area is also critical to this process. These should include standardised clinical outcome measures to evaluate change in movement quality, linking the BSF and Activity domains of the ICF following treatment, the use of condition specific quality of life measures and standardised participation measures which capture both a child's attendance and involvement in activities

Mixed methods research designs are essential to capture evidence to evaluate the impact of BoNT-A treatment. Carefully selected but comprehensive quantitative data can be collected throughout the ICF domains, allowing the evaluation of multiple outcomes simultaneously in conjunction with qualitative data to provide insight into the child and family experience. Future research should also include sufficient participant numbers so that studies with multiple outcomes are adequately powered to enable meaningful statistical analysis to be performed.

As BoNT-A is recognised as an accepted modality in the treatment of spasticity in CP, the introduction of control groups and withholding of treatment can present ethical dilemmas and result in difficulties with recruitment. Therefore, high quality longitudinal studies with rigorous study designs, using children as their own controls could serve to address many of these issues.

Combining quantitative and qualitative perspectives can provide insight into the impact of BoNT-A treatment as part of a complex rehabilitation programme. The findings of such studies may be more applicable within clinical settings than identifying change scores on a single outcome variable in a highly controlled research setting. Longitudinal studies are required to provide meaningful information on the long-term effect of BoNT-A treatment. This is especially pertinent with the current concerns regarding the long-term effects of repeated BoNT-A use on muscle morphology.

Chapter 3 Research Outline

3.1 Aims and objectives of the PhD

Having considered the literature discussed in Chapter 1 of this report, together with the results of the systematic review in Chapter 2, gaps in knowledge regarding the efficacy of BoNT-A use were highlighted. Although there was consistent evidence to show that BoNT-A reduced hypertonia, results demonstrating changes in activity, participation or QOL associated with BoNT-A treatment were mixed, with uncertainty about how long any observed changes last. The majority of studies reporting improvement following BoNT-A within the systematic review did not evaluate change beyond six months (Kelly et al., 2019, Thomas et al., 2016, Wright et al., 2008). It was apparent that further investigation into CYPwCP's response to BoNT-A treatment throughout all domains of the ICF was warranted.

In conducting this PhD research, the researcher aimed to contribute to this evidence base by investigating the multidimensional response to BoNT-A treatment in ambulant CYPwCP within all domains of the ICF over a 12-month period using standardised outcome measures in an established tertiary level service. It has also been suggested that standardised outcome measures may not be sensitive enough to pick up change following BoNT-A treatment and may not reflect the changes observed by children and their families (Bjornson et al., 2007, Wright et al., 2008). This evidence was therefore, further supplemented, by the introduction of a novel validated outcome tool the Quality Function Measure (QFM), in order to evaluate change in movement quality (considered an essential component of effective gross motor skills in children with CP) following BoNT-A use. This is the first reported use of QFM within the literature associated with BoNT-A use in CP.

Research questions

The objectives of this research were to:

1. Investigate clinical and patient reported outcomes (of body structures and function, quality of movement, activities and participation and health-related QoL) associated with lower limb BoNT-A injections in ambulatory CYPwCP over a twelve-month period.
2. Determine the factors associated with a response to BoNT-A treatment (such as age, GMFCS Level, previous injection history and injection pattern)
3. Explore families' experience of BoNT-A treatment and investigate how standardised clinical outcome measures relate to child and parent perceptions of response following BoNT-A treatment.

To achieve these objectives a mixed methods study was conducted comprising of two phases:

Phase I: To meet objectives 1 and 2: a prospective longitudinal study using a one group repeated measures design with each child acting as their own control.

Phase II: To meet objective 3: interviews were conducted with a subgroup of CYPwCP and parent/carers from Phase I to elicit their experiences, and views of change following BoNT-A treatment.

3.2 Study design

A pragmatic prospective observational mixed methods longitudinal study was chosen to investigate clinical and patient reported outcomes associated with lower limb BoNT-A injections in CYPwCP. Participants needed to be aged between 4-18 years with a confirmed diagnosis of ambulatory cerebral palsy (Gross Motor Function Classification System (GMFCS) level I, II or III). Patterns of response to BoNT-A over a 12-month period needed to be identified within all domains of the

ICF: Body Functions and Structures, Activity and Participation, together with Quality of life (QOL).

As BoNT-A treatment was considered best practice care for focal hypertonia management in CP (Barber et al., 2014, Fehlings et al., 2010, Novak et al., 2020, Wallen et al., 2007) there were practical and ethical concerns regarding the inclusion of a 'no treatment' control group and so a comparator was not considered ethically appropriate. As this study was a longitudinal repeated measures design, each participant acted as their own control.

The study used a convergent design mixed methods approach (Creswell and Creswell, 2013). The results from the quantitative data collected in Phase I of the study (Chapter 6-Chapter 8) were combined with the findings from the qualitative data in Phase II gathered from semi-structured interviews with CYP and their parents (Chapter 11) and are synthesised in Chapter 12. A mixed method approach was chosen to provide a comprehensive means of researching this topic, recognising that the analysis of a combination of both quantitative and qualitative data provided a '*better understanding of the research problem than either trends alone*' (Creswell and Plano Clark, 2011).

The advantage of using mixed methods research when evaluating interventions in cerebral palsy is in the thoroughness of findings generated by using both quantitative and qualitative approaches (Zoellner and Harris, 2017). This provided a more complete picture by which to understand the role of BoNT-A in the management of hypertonia in ambulant CYPwCP. It has been argued that using only quantitative methods can produce results which may not reflect the experiences of CYPwCP and using only qualitative methods may not reflect the experiences of the wider population (Pope and Mays, 1995). Using both types of data allowed for weight to be given to the experiences and views of children and their families. This research has contributed to the existing evidence-base and provided a much-needed voice of both parents and CYP, particularly the voice of the child with CP which is rarely heard in the literature.

It was recognised that the success of mixed methods research lies in the process of integrating the findings from both approaches (Johnson et al., 2007, Timans et al., 2019). This study followed a parallel analysis approach (Teddlie and Tashakkori, 2011, Zoellner and Harris, 2017), where data from each phase of the study (Phase I quantitative and Phase II Qualitative) was analysed and reported individually. Adopting this method enabled comprehensive analysis of each dataset leading to the identification of key results. These findings were enhanced by the comparison and analysis of both quantitative and qualitative data at the final stage of the analysis in Chapter 12, leading to triangulation and a cross-validation of results with inferences about convergence and divergence of Phase I and Phase II conclusions.

3.3 Ethical considerations

3.3.1 Risks and burdens to participants

There were no anticipated intrusive risks or excessive burdens introduced by taking part in any part of this research. It was acknowledged that participation may have been demanding of each participant's time. In order to minimise any extra burden on CYP and their families time, Phase I of this study mirrored usual clinical practice within the GOSH Botulinum Toxin Service. All standardised physical assessments were kept the same as per usual clinical practice. All treatment and assessments continued with the same clinical team.

The additional standardised outcome measure the Quality Function Measure (QFM) introduced for the study was scored by the researcher at a later date from the video recording of the Gross Motor Function Measure (GMFM) which formed part of the child's usual clinical practice assessment. This did not result in any extra burden for the CYP.

In phase I two additional questionnaires were added to clinical assessment processes for the study period. The Participation Environment Measure - Children and Youth (PEM-CY) and The Cerebral Palsy Quality of Life Measure (CPQOL). Families were advised that these questionnaires differed from current clinical

practice and parents were given the opportunity to complete it during their child's appointment or at home depending on preference.

Phase II of the study involved a subset of families from Phase I who took part in an audio recorded semi-structured interview. This required an additional interview with parents and CYP. Families were offered the option of the interviews taking place at the hospital or in their own home to minimise inconvenience. For families opting for hospital interviews, the burden was minimised by co-ordinating the interviews with a visit to the hospital for a clinical appointment.

Procedures were in place so that in the event of any issues of concern being raised by either the CYP or their parent these would be dealt with as regards to usual safeguarding and clinical practice. However, no concerns were raised at any time during the study.

3.3.2 Potential benefits to participants

There were no direct benefits to participants for taking part in this study. Although participants and their families have had access to the final results of this study. These study findings will affect their future treatment with BoNT-A as well as future users of the service.

Participants who took part in Phase II shared views about their experience of receiving treatment and its impact on their life. This gave families the opportunity to explore whether standardised outcome measures reflected their views on any changes that occur after BoNT-A injections.

3.3.3 Confidentiality and Data Monitoring

Personal data stored in paper and other manual files were appropriately filed and stored securely as per usual GOSH policy (Appendix 14.1). Audio and Visual recordings were uploaded onto secure password protected encrypted NHS computers and deleted from the recording device immediately after uploading. Anonymised data were held on a secure encrypted, password protected UCL laptop.

Personal identifiable details and consent forms were stored separately to research data. When data were collected as a hard copy, e.g. consent forms and questionnaires these were stored in The Movement Disorders Service at Great Ormond Street Hospital as soon as this was practicable. Electronic data were stored on password protected servers accessed through computers/encrypted laptops. All transcripts were anonymised, and personal identifiable details were kept in separate files to research data. The data were held at Great Ormond Street Hospital as per Hospital and R&D policy. Appropriate access controls were in place at GOSH to ensure that access to confidential research information was restricted to those who needed access such as the researcher (LK) and clinical team (LK was also part of the clinical team).

LK ensured the confidentiality of personal data by following the NHS Code of Confidentiality (Appendix 14.1). The study had an information sharing protocol (Aldridge et al., 2010) that was adhered to by all members of the research advisory team and the transcription service used to transcribe the interviews (Take Note Typing™). The study protocol was reviewed and approved by the Research and Development team and Caldecott Guardian at Great Ormond Street Hospital. All participants were allocated a participant number which was used on all documents or data relating to them instead of their name. Pseudonyms were used in all reports and publications and direct quotations were anonymised.

3.3.4 Ethical approval

Approval for this study (#IRAS 211617) was granted by London Central Research Ethics Committee on 4th May 2017 (#REC 17/LO/0579). This study was registered with the joint research and Development office at GOSH and UCL GOSH Institute of Child Health (# 15HN07) with HRA approval granted on 29th June 2017 and was adopted onto the NIHR Clinical Research Network Portfolio (Appendix 14.1). As this was an original study all documentation was specifically developed by LK (Appendix 14.2).

3.4 Study sample and setting

The study was undertaken in a paediatric tertiary referral hospital Great Ormond Street Hospital for Children, London, UK. Ambulant CYPwCP (GMFCS Levels I-III) fulfilling the eligibility criteria (Table 3-1) were enrolled from the Movement Disorders Service, a clinical service which assesses children's suitability for BoNT-A injections. The study used a convenience sample in which children who were due to receive BoNT-A treatment were enrolled sequentially until a balanced number of children within the three GMFCS levels was reached.

Inclusion Criteria CYP	Exclusion Criteria CYP
Confirmed diagnosis of CP (Unilateral or bilateral CP) with dynamic hypertonia (spasticity+/or dystonia)	History of previous orthopaedic surgery to the injected muscle
GMFCS level I,II or III	History of previous neurosurgery for tone reduction (Selective Dorsal Rhizotomy)
4-18 years old	Lower limb BoNT-A in previous 6 months
Requiring lower limb BoNT-A for dynamic hypertonia interfering with lower limb functional goals or causing pain	Unrelated musculoskeletal problems, such as recent acute injury, or congenital structural deformity
Access to a block of physiotherapy from local team following BoNT-A (minimum of six weekly sessions)	Contra indications to BoNT-A treatment
	Unable to complete baseline assessments due to capacity, ability or willingness
Exclusion Criteria -Parents	
Inadequate knowledge of English language to complete outcome measure despite the use of interpreters	

Table 3-1 Eligibility criteria for The Toxin Study

The target sample size for Phase I of the study was 60 CYPwCP, (20 from each of the GMFCS levels I, II and III) aged 4-18 years attending the Motors Disorder Service at Great Ormond Street Hospital for Sick Children (GOSH). A subgroup of 18 CYP (≥ 5 from each of the GMFCS levels I-III) together with their parents was considered a large enough sample size to participate in the qualitative element (phase II) of the study following review at six months post injection. Eligible CYP were consecutively

recruited using a sampling matrix to ensure diversity of age, GMFCS level and treatment outcome until a balanced sample was achieved.

3.4.1 Sample size calculation

Phase I

Sample size for Phase I was determined with the support of Statistical Support Service (SSS) at UCL Great Ormond Street Institute of Child Health.

As this study was the first reported use of QFM as a primary outcome measure following BoNT-A, no data existed to inform a power calculation. It was anticipated that the results from this study would provide data for power calculation in future multi-centre trials. The study was therefore powered to detect a difference on the second primary outcome measure: The Canadian Occupational Performance Measure (COPM). The sample size power calculation was based on anticipated change in the COPM goal performance at the primary end point T1 (6 weeks post intervention) after BoNT-A treatment. A change in score of two or more points on the performance scale of the COPM was considered clinically meaningful (Law et al., 2005, McColl et al., 2005). A previous study of lower limb BoNT-A use in CYPwCP generated standard deviations between 1.4 and 1.7 for COPM performance (Bjornson et al., 2007). Therefore, based on a moderate estimate using a mean change of two points on the COPM performance scale (power 0.8, two tailed, $p < 0.05$), 36 participants (12 in each GMFCS level) were required.

Attrition is a recognised problem in longitudinal research designs with either intermittent (participants unavailable for one/more measurement time points) or permanent attrition (participant drops out) (Mazen et al., 2019). Rates vary across the literature, and a meta-analysis of 92 longitudinal studies examining personality traits reported a 44% average attrition rate across the studies (Roberts et al., 2006) whereas other areas have reported as high as 85% attrition for vulnerable populations (Garnier-Villarreal et al., 2014). Therefore, allowing for attrition and

missing data over a twelve-month period a total of 60 participants (~20 in each GMFCS level) were planned for recruitment for Phase I of the study.

Phase II

A sample size of 18 children and young people (at least 5 from each of the GMFCS levels I-III) and their parents (a subgroup of Phase I) was determined to be sufficient to participate in the qualitative element of the study. This sample size was in line with qualitative research where the aim is to obtain rich in-depth data (Fugard and Potts, 2015).

Methods of data collection for Phase I and II have been detailed in Chapter 4 and Chapter 10 respectively.

Chapter 4 Phase I – Quantitative study methodology

This chapter summarises the methodology used in the Phase I study and outlines the assessments used to collect outcome throughout the 12 months of the study.

4.1 Study procedure and data collection

4.1.1 Recruitment

Eligible participants were identified by the researcher from clinic lists of the Movement Disorders Service at GOSH. A member of the clinical team (not involved with the study) explained the study to the family. They were then provided with an invitation letter and parent and CYP information sheet (PIS). Parents and CYP were given at least 24 hours to consider if they would like to participate. Prior to data collection, parents were asked for written informed consent for their own and their child's participation in the study. CYP were asked to give their assent to participate, and a selection of assent forms were available depending on age, level of maturity and cognitive ability (Appendix 14.2).

At the time of taking consent parents were asked if they would like to receive PIS about the qualitative interviews in Phase II of the study. A separate consent/assent form was used for Phase II of the study. Agreement to take part was reconfirmed at each contact.

CYPwCP recruited into the study proceeded through the Movement Disorders Service at GOSH in the usual way, according to standard clinical practice. All decisions regarding clinical care, assessment frequency and BoNT-A injections continued as per usual clinical practice. Standardised clinical assessments and outcome measures were performed at four assessment time points T0 -T3 (Table 4-1).

Assessment point	Timing	Comments
T0	Pre-injection baseline measures	1- 6 weeks before injection
T1	6 weeks post injection	Estimated time to reach target threshold for BoNT <i>'Evaluation of efficacy of injections'</i>
T2	6 months following injection	Expected completion of pharmacological action <i>'Evaluation of retention of effects post injection'</i>
<p><i>At T₂ there were three possible outcomes for patients (as per usual clinical practice)</i></p> <ul style="list-style-type: none"> • Favourable response to injections with retention of effects– no further injections indicated at this time • Favourable response to injections without retention of effects- listed for a second injection episode within 12 months <ul style="list-style-type: none"> • No favourable response to injections- discharged to other services (e.g., neurosurgery/orthopaedics) 		
T3	12 months following initial injection	Final assessment <i>'Evaluation of retained long term effects'</i>

Table 4-1 Timings of study assessments T0-T3

All participants who had not undergone surgical intervention were assessed at T₃, independent of outcome at T₂. This facilitated the analysis of factors associated with changes in impairment, activity, participation and QOL following BoNT-A treatment and time to re-injection over 12 months. The need for re-injection was determined by clinical examination (documentation of a technical response in the muscle (e.g.,

reduction in spasticity), evaluation of goal attainment (COPM) scores and in consultation with families and local team as per usual clinical practice.

4.1.2 Validated outcome measures for all ICF domains

The standardised outcome measures used in the study are summarised within the ICF domains in Figure 4-1 and administration details of the measures are summarised at the end of the chapter in Table 4-2. Outcome measures followed GOSH standard clinical practice with additional measures introduced specifically for the study highlighted in red in Table 4-2. Patient assessment took between 60-90 minutes as per usual clinical practice.

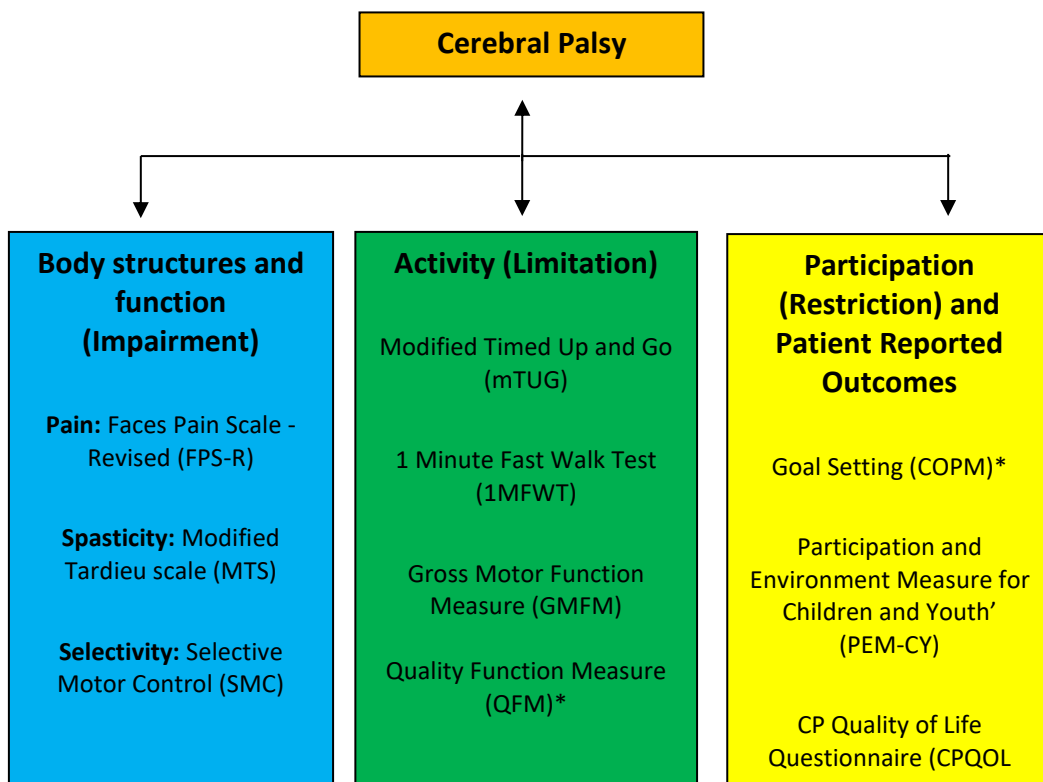


Figure 4-1 Study Outcome Measures within ICF Domains

4.1.3 Training and fidelity

All clinical staff who collected study data were experienced members of the tertiary service with extensive experience of working with children with CP (mean 21 years, range 13-33 years). A standardised measurement protocol was already in place in the clinic and an additional study manual with instructions for clinicians was developed by LK to ensure consistency (Appendix 14.3).

Two half day training sessions took place for clinicians collecting study data prior to start of recruitment in September 2017. Monthly meetings with clinicians ensured consistency and adherence to study protocol.

4.1.4 Data collection- clinical assessment

Collection of baseline clinical information (standard clinical practice)

Information regarding classification of CYPwCP relative to CP type and GMFCS level (1.3.1), demographics including age, co-morbidities, cognitive ability, therapy, and orthotic provision were collected. All children were scheduled for a six-week block of targeted goal directed therapy delivered by their usual community therapy teams in the post injection period. Any additional interventions such as casting and change in orthoses following BoNT-A together with additional participation in activities were recorded in the clinical notes.

BoNT-A assessment (standard clinical practice)

An experienced multidisciplinary team consisting of a consultant doctor and senior physiotherapist identified the muscle groups to be injected. Muscle selection varied between participants according to spasticity-related functional impairment. This was based on clinical assessment with reference to standard definitions (Graham et al., 2016) and treatment was related to the goals of the CYPwCP and family.

The lower limb muscle groups injected were categorised into three groups: distal, proximal and multilevel. These were defined as 'distal' involving muscles that insert

below the knee joint, 'proximal' in muscles that originate above the knee joint and 'multilevel' if both distal and proximal muscles were treated (Figure 4-2).

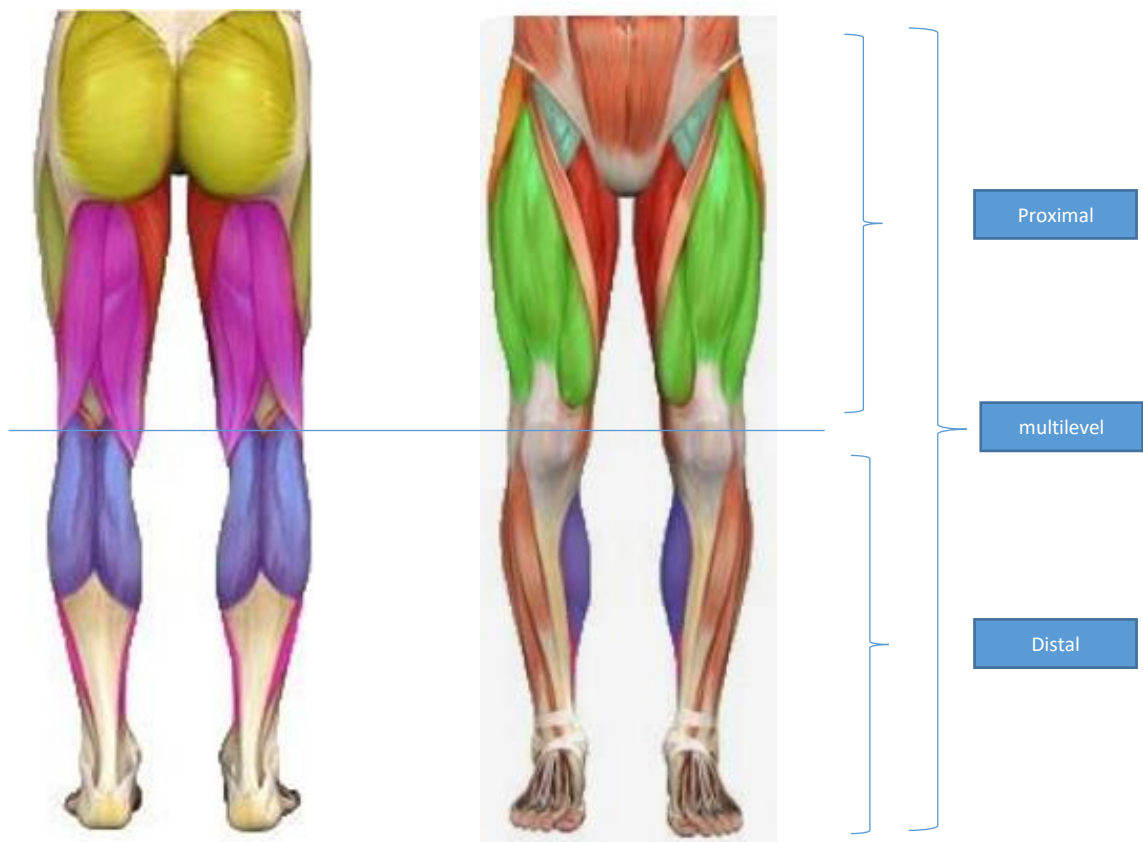


Figure 4-2 Categorisation of injected lower limb muscle groups: proximal, distal and multilevel.

4.1.1 Administration of BoNT-A

BoNT-A was prescribed as per standard clinical practice at GOSH using abobotulinumtoxinA, Dysport® Ipsen Ltd. Administration is 500 U Dysport® diluted in 1 ml of normal saline, up to a maximum dose of 30 units /kg /body weight or a total dose up to a maximum of 1000 units per injection session. All CYPwCP received BoNT-A injections under ultrasound guidance as a day case with oral sedation and local analgesia. Adverse events were recorded and standard reporting and follow up was as per current GOSH policy.

4.2 Data collection- study outcome measures

4.2.1 Primary outcome measures

The Quality Function Measure (QFM)⁶ is an observational criterion referenced measure designed to evaluate the quality of movement in standing and walking skills in children with CP. It is used in conjunction with the Gross Motor Function Measure (GMFM) using Dimensions D and E, which focus on 'standing' and 'walking, jumping and running skills'. The GMFM is considered a 'gold standard' tool for evaluating gross motor function in children with CP, evaluating 'how much' of a gross motor skill a child can perform (Boyce et al., 1995, Russell et al., 2000). However, there are concerns that GMFM alone is not sensitive enough to pick up meaningful change post intervention, due to 'ceiling effects' of the measure when used with ambulant CYPwCP in GMFCS levels I-III (Love et al., 2010b, Tustin et al., 2016, Wright et al., 2014a). The QFM scores movement quality and assesses 'how well' a child performs gross motor tasks (Wright et al., 2014a). It has shown excellent rater and test-retest reliability (ICC 0.89-0.97, $p < 0.001$). Minimal detectable change estimates (9-11 %) suggest that the scale has potential as an evaluative measure (Tustin et al 2016; Wright personal communication 2018). However to date, there are no published studies evaluating the responsiveness of QFM post BoNT-A.

The QFM is performed by taking videos of up to 3 trials of dimensions D (13 items) and E (24 items) of the GMFM following a standardised protocol to record movement in the frontal and sagittal plane (Children in GMFCS levels I and II need to complete a minimum of 13 items to score GMFM-66 within D and E dimensions and children in GMFCS III need to complete a minimum of 5 items as recommended within the GMFM-66 manual (Russell et al., 2000)).

QFM certification requires clinicians (*raters*) to undertake a one day in person QFM training workshop and approximately 10 hours of group scoring before independently passing the QFM video scoring criterion test administered by the test

⁶ Primary outcome measure for The Toxin Study

developers (criterion level, weighted kappa >.80 for agreement with test developer, see Appendix 14.4 for example of criterion scoring). The researcher (LK) has been accredited twice on QFM testing, once prior to the study commencing and once mid data collection and was in close contact with the test developers throughout the study. During pilot data collection this study highlighted some operational ambiguities in administering the scoring criteria and these were highlighted to the test developers and subsequently changed in the updated version of the manual.⁷

Regular contact regarding scoring was also maintained with test developers during the four month scoring period to minimise 'observer drift' (a reported phenomenon where raters change the way in which they apply scoring criteria over time (Kobak et al., 2004)). This was also controlled for by randomised order of scoring as described below so that 'drift' would not differentially influence data across the different assessment phases (Kazdin, 1977).

Each video was later scored by the researcher (mean time to score ~ 60 minutes, range 30-90 minutes, Tustin et al 2016) to obtain percentage scores for 5 Quality attributes: Alignment, Co-ordination, Dissociated movement, Stability, and Weight shift. The GMFM was carried out in clinic as per usual clinical practice but for the study this was video recorded as part of the participants' clinical record.

In order to minimise bias, LK was blinded to the stage of treatment of each child (i.e. pre or post injection). To conceal these time points each video containing GMFM D & E (standing and walking) dimensions was anonymised, and date of recording was not visible and each video session was randomly allocated a letter by a co-worker not involved in the service. This ensured that the researcher was masked to the child's assessment time point. To minimise recall bias, videos of at least 10 other children were scored before scoring the video of the same child at a different time point. This was in keeping with previous QFM reliability studies which suggested a gap of two weeks before evaluating test-retest scores (Wright et al., 2014, Tustin et al., 2016). Raw item QFM scores were converted into QFM attribute

⁷ Item # 64 Standing: picks up object from floor, arms free, returns to standing

summary scores using an Excel database supplied by the test developers. Data for each participant at each assessment time point was entered into a secure data base without access to previous scores until scoring for all assessment time points was complete.

QFM inter-rater reliability had already been established within the service for a previous study with ambulant CYPwCP undergoing selective dorsal rhizotomy (SDR) surgery. ICC estimates were excellent for all QFM attributes (0.95-0.99, $p < 0.001$) with lower Confidence Intervals (CI) beyond 0.9 for all QFM attributes apart from Weight shift (lower CI: 0.8) suggesting good to excellent level of reliability for all attributes.⁸

As the QFM is a novel outcome measure there is little information about the psychometric properties of the measure, therefore intra-rater reliability was determined for the study. Although no formal consensus exists as to what constitutes adequate reliability for an outcome measure, guidelines suggest that reliability coefficients greater than 0.89 are considered important to guide care at the individual participant level whilst coefficients of ≥ 0.7 are considered acceptable for group research (Matheson, 2019).

Twelve videos were scored a second time by LK after a minimum of a 4-week period from the original scoring, without reference to previous scores. At least 10 other videos from different children were rated between the first and second rating for the repeatability test.

Intra-rater reliability for QFM attribute scores were evaluated using an intraclass correlation coefficient (ICC). In view of the single-rater study design and a desire to generalise beyond the involved rater (LK), an ICC type 2:1, 2-Way Random effects single measure model of absolute agreement was chosen (Shrout and Fleiss, 1979). The 95% confidence interval was constructed for each ICC attribute point estimate

⁸ ICC in published studies. Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability (Koo and Li, 2016).

to enable confidence in the calculated coefficient. However, as it can be difficult to interpret ICCs clinically due to their dimensionless value (Koo and Li, 2016), concordance between the measurements was also supplemented by two other methods; Bland Altman methods (Bland and Altman, 1986) were used to assess within rater agreement, and Standard Error of Measurement (SEM) was also calculated (Chapter 6 (6.1.5.2)). As SEM is expressed in the same units as the measurement scale it is said to be easier to interpret clinically (Bruton et al., 2000). SEM was determined using the formula $SEM = SD\sqrt{1-ICC}$. Following this SEM values for the study were used to estimate the minimal detectable change of each QFM attribute at 95% confidence level using the equation $MDC_{95} = SEM \times \sqrt{2} \times 1.96$ (Walker et al., 2018).

Canadian Occupational Performance Measure (COPM)⁹ is a goal attainment tool modified for use in the paediatric population (Law et al., 1995a, McColl et al., 2005). It identifies concerns regarding 'occupational performance' i.e., the ability to carry out functional tasks and has been used to document change post BoNT-A rehabilitation (O'Neil et al., 2003, Thomas et al., 2016). Used widely in the paediatric population, areas of concern regarding a child's self-care, activity and leisure are explored during a semi-structured interview between the child, family and clinical team. COPM has demonstrated high re-test reliability (ICC 0.76-0.89), good content, construct and criterion validity and sensitivity to change for children with CP receiving BoNT-A (Cusick et al., 2006, Fragala et al., 2002).

COPM use was well established in the clinical team at GOSH and has been used to evaluate goal attainment for over ten years. Families were asked to identify up to three areas of concern which they and their child hoped to improve following lower limb BoNT-A injections. In order to make the goals meaningful, whenever possible these goals were set with the child's input (Bjornson et al., 2007, Verkerk et al., 2021).

⁹ Primary outcome measure for The Toxin Study

Children and parents rated their perception of the child's current performance and their satisfaction with this performance on a 1–10 ordinal scale. The individual goals identified by each child were given two baseline scores; COPM Performance (COPM-P) which evaluated the pre BoNT-A treatment evaluation of goal performance and a COPM Satisfaction score (COPM-S) which evaluated how satisfied the CYPwCP and their families were with that goal performance at the time of the assessment. COPM-P and COPM-S scores were evaluated at each post BoNT-A assessment time point and re-scored (1-10).

Reflective scoring, (showing families the results of their baseline assessment) was used, as this method has been shown to improve the discriminatory power of the COPM to evaluate change over time (Eysen et al., 2011).

A score change of two or more points has been described as a minimal clinically important difference and was considered in this study to be a clinically significant improvement (Kang et al., 2020, Law et al., 2019, McColl et al., 2005). Whilst it was anticipated that children's goals could change throughout the study, only the original goals set at baseline were evaluated in terms of the study

4.2.2 Secondary outcome measures

Modified Tardieu Scale (MTS) is a recognised clinical measure used to differentiate dynamic spasticity from fixed contracture in a muscle. It determines the passive range of movement at two different movement velocities; fast (R1) which is referred to as the 'dynamic catch' in the muscle and is considered a proxy measure for the presence of spasticity, and slow (R2), which provides information about the presence of fixed or dynamic contracture in the muscle.¹⁰ The relative difference between the two (R2-R1) determines the 'dynamic component' of the muscle contracture (see Figure 4-3). The presence of a 'dynamic catch' as measured by R1

¹⁰ A dynamic contracture in a muscle is defined as one that can be corrected to neutral position with a maximal or submaximal force as opposed to a static (fixed) contracture which cannot be corrected to a neutral position.

is an indicator for treatment of spasticity with BoNT-A injections (Boyd and Graham, 1999, Love et al., 2001, Strobl et al., 2015). It is measured in degrees with a universal goniometer with the child positioned in standardised positions for each muscle (Appendix 14.3). It has been shown to be more effective than the Modified Ashworth Scale (MAS) in identifying the presence of spasticity (88.9%, kappa= 0.73, p=0.000) and the presence of contracture (77.8%, Kappa=0.503, p=008) and the severity of contracture r=0.49, p=0.009) (Alhusaini et al., 2010, Boyd and Graham, 1999), with good to excellent reliability reported for MTS R1 with ICCs between 0.86 and 0.91 (Numanoğlu and Günel, 2012).

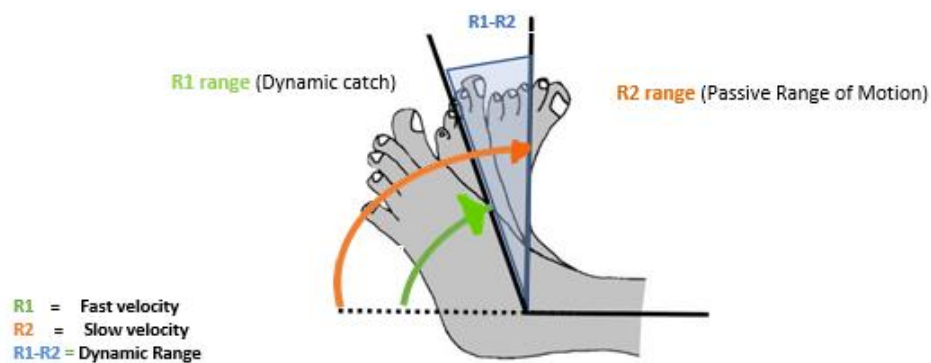


Figure 4-3 Diagrammatic representation of the Modified Tardieu Scale (MTS)

Modified Ashworth Scale (MAS) is another accepted clinical tool, frequently used in clinical practice and research in the adult population to measure spasticity, but less so in the field of paediatric cerebral palsy, where it is mostly used for research purposes (Love et al., 2010b). It has a six point rating system which grades muscle spasticity (0,1,1+,2,3,4) measured in the same standardised positions as MTS (Appendix 14.3). However unlike MTS there appears to be limited validity in children with cerebral palsy (Bar-On et al., 2013, Fosang et al., 2003, Mutlu et al., 2008) and it is unable to differentiate between neural and non-neural causes of spasticity (Alhusaini et al., 2010). Despite its limitations, due to its widespread use in the literature on BoNT-A use in paediatrics (Blumetti et al., 2019), it was included as a supplementary spasticity measure in this study permitting comparison with published findings.

Selective Motor Control (SMC) is considered a good discriminator of selective motor control and assesses a child's ability to voluntarily and selectively control the dorsiflexors of the ankle. It is measured by an ordinal scale between 0 and 4. Children were measured in standardised position as per test developer's instructions (Boyd and Graham, 2007). A higher score indicates better selectivity, inter-rater agreement has been shown to be moderate ($Kw = 0.58-0.77$) with strong test-retest reliability ($Kw=0.88-1$) (Lowling et al., 2010).

Faces Pain Scale–Revised (FPS-R) is a self-report measure used to assess the intensity of children's pain and is validated for use with children aged 4 years and older (Hicks et al., 2001). It consists of seven faces corresponding to a 10-point linear scale (Figure 4-4). Face scales are generally preferred, especially by younger children, to visual analogue and word descriptor scales (Johnston and von Baeyer, 2012). The FPS-R has the advantages of having no smiling face and no tears, which is said to avoid the confounding of affect and pain intensity and other complicating effects of these 'anchors' particularly with younger children (Chambers and Craig, 1998). Its validity is supported by a strong positive correlation ($r=0.93$, $N=76$) with a visual analogue scale (VAS) measure in children aged 4-16 years and coloured analogue scale (CAS) ($r=0.84$, $N=45$) to rate pain during hospitalization for surgical and non-surgical painful conditions (Hicks et al., 2001). A change score of >2 points is reported to represent a minimal clinical important difference

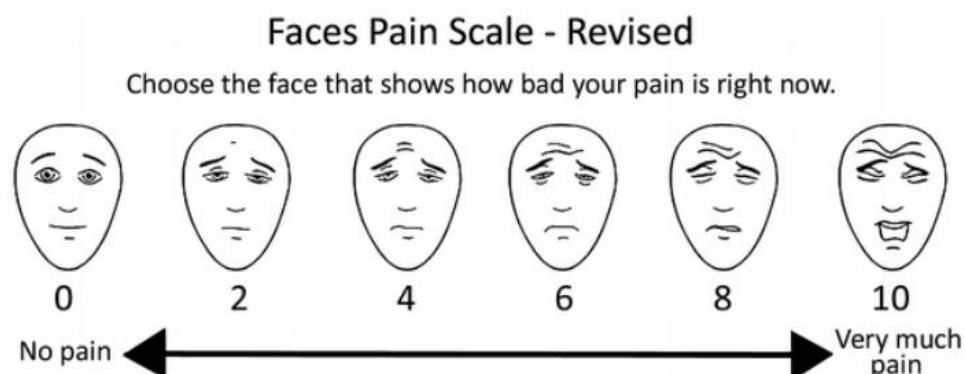


Figure 4-4 Faces Pain Scale

Gross Motor Function Measure (GMFM-66) is considered a 'gold standard' clinical and research tool used to evaluate gross motor function in CYPwCP. It includes 66 gross motor tasks grouped into five dimensions: A) Lying and Rolling; B) Sitting; C) Crawling and Kneeling; D) Standing; and E) Walking, Running and Jumping. Only dimensions D and E were used for the purposes of the study. Each item is scored using a 4-point criterion referenced scoring system on a 0-3 ordinal scale representing the degree of task achievement specified by item specific criteria. A maximum of three trials were permitted per GMFM item (see QFM details). Any omitted items were scored "not tested". Ordinal GMFM item scores were converted into interval level GMFM-66 data using the Gross Motor Ability Estimator - second edition (GMAE-2, 2013) software available from test developers. GMFM-66 has been shown to have high test-retest reliability (ICC 0.99) (Russell et al., 2000) and be more responsive to change than the original GMFM with 88 items (Wang and Yang, 2006), with less of a ceiling effect (Damiano et al., 2005).

One Minute Fast Walk Test (1MFWT) is considered a good discriminator of functional ability for dynamic balance, muscle performance and endurance (McDowell et al., 2005). Children were asked to walk for 1 minute along a 9-metre corridor at maximum speed without running. Children were able to use usual walking aids and orthoses and the presence of these were recorded to aid repeatability of testing conditions. Distance was calculated to the nearest 10cm. 1MFWT shows concurrent validity with GMFM with significant correlation between GMFM score and distance walked ($r=0.92$) and excellent reliability (ICC0.97)(Scholtes et al., 2012).

Modified Timed Up and Go (mTUG) is considered a good discriminator of balance, anticipatory postural control, and functional mobility in CYPwCP. Children were timed rising from a chair, walking 3 metres, touching a star on the wall, and returning to sit down as quickly as they could without running. Children were able to use usual walking aids and orthoses and details were recorded at baseline and repeated at each assessment time point. The child was given the opportunity to repeat the test three times and the best score was recorded. The measure has been

shown to differentiate performance between children at GMFCS levels I-III. It has shown good to excellent inter-rater reliability (ICC 0.83-0.99)(Carey et al., 2016, Williams et al., 2005).

Participation Environment Measure- Child and Youth (PEM-CY) is an innovative-parent reported participation measure for use with CYP between 4-18 years. It is the first reported measure to examine children's participation in all three areas of a child's life; home, school and community. It also takes into account the environmental challenges. There are three sections: Home (10 items), School (5 items) and Community (10 items). Whilst the questionnaire is a generic paediatric tool and not specific to CYPwCP it has shown good internal consistency (ICC 0.72-0.83) and test-retest reliability (ICC 0.76-0.89) with a variety of different disabilities including CP as well as with typically developing children (Coster et al., 2011).

Participation is a complex, multifaceted construct and it has been recognised that there are two components of participation as defined by the ICF "*attending and being involved in life situations*" (WHO, 2007). Therefore, two domains of the PEM-CY were selected for analysis; *Average frequency* of participation in activities, which reflect both the attendance and range of activities that a child is involved with and *Average involvement* in these activities which reflects the experience of a child's participation whilst carrying out these activities. Average frequency and Average involvement were analysed in three settings; home, school and community.

Cerebral Palsy Quality of Life (CPQOL) is a QOL assessment administered by questionnaire, specifically designed for CYPwCP. It quantifies 'well-being' across seven key QOL domains. Items are scored on a nine-point rating scale, then summed and averaged to generate seven domain scores in the following areas:

- Social wellbeing & acceptance
- *Feelings about functioning**
- *Participation & physical health**

- Emotional wellbeing & self-esteem
- Access to services
- ***Pain & impact of disability****
- Family health

There are two CYP reported and two proxy reported versions dependent on CYP's age and cognitive ability (CPQOL-Child, CPQOL-Teen). All have demonstrated good internal consistency (Child ICC 0.74-0.92; Teen 0.81-0.96) and test-retest reliability (Child ICC 0.76-0.89; Teen 0.59-0.83) (Davis et al., 2013, Waters et al., 2007).

The CPQOL developers have stipulated a minimum cognitive age of 9 years for child self-reporting. Due to previous service evaluation of age and cognitive ability of CYPwCP using the service, it was anticipated that the majority of the children would be unable to self-report. The proxy reported versions were therefore used throughout the study to ensure consistency of reporting. However, all families were encouraged to complete these questionnaires in consultation with their children, to encourage collaborative reporting (Brewer et al., 2014).

Three domain scores considered most pertinent to evaluating BoNT-A intervention were selected a priori*; 'feelings about functioning', and 'participation and physical health' were selected as most representative of function and participation and these were both used in multilevel regression analysis for this study. The pain and impact of disability domain scores were also analysed and have been reported in conjunction with mFPS pain score used in the study.

All the outcome measures used for the study are summarised in Table 4-2. The outcomes introduced specifically for the study in addition to usual outcome measures have been highlighted in red.

ICF	Measuring	OUTCOME MEASURES	MEASUREMENT	LEVEL	Explanation
Body functions and structures (impairment)	Spasticity and dynamic range of movement	Modified Tardieu Scale (MTS) (Boyd and Graham, 1999)	Standardised goniometry placement	Degrees	MTS measured at injected muscles. The difference between the slow stretch R ₂ and a fast stretch R ₁ = 'dynamic range' and is reported to be amenable to treatment with BoNT-A FPS-R which has been shown to have good psychometric properties for pain reporting (modified for use by carer when CYP unable to self-report)
	Pain	Faces Pain Scale (FPS-R) (Hicks et al., 2001)	Score assigned by CYP	Score out of 10	
Activity (functional limitation)	Gross motor function	Gross Motor Function Measure (GMFM) (D&E walk/run/jump dimensions) (Russell et al., 1989)	Video recorded** Standardised assessment form Scored by clinician	% score	The GMFM designed to evaluate change in gross motor function over time in children with cerebral palsy. It is the standard outcome assessment tool for clinical intervention in CP <i>Families are consented for video storage in accordance with the Great Ormond Street Hospital policy</i> The Quality FM observational validated measure captures the quality of movement of the GMFM (D&E) as above post BoNT-A may be more sensitive to change than GMFM alone <u>scored from video no extra assessment time for CYP</u> mTUG integrates transitions and walking skills, and provides a meaningful measure of capability. It has been shown to be a reliable outcome measure for assessing functional mobility in CP children. 1MFWT a good discriminator of functional ability for dynamic balance, muscle performance and endurance.
	Quality of Gross Motor Function	Quality Function Measure (QFM)** (Wright et al., 2014)	** scored by PI later from GMFM above	% score for 5 quality attributes	
	Balance	Modified Timed up and Go Test (mTUG) (Dhote et al., 2012)	Timed standardised test (from sitting CYP stands and walks distance 3m touches star returns to seat)	Seconds	
	Walking ability (Efficiency)	1 minute fast walk test (1MFWT) (McDowell et al., 2005)	Distance recorded (5 minutes rest, followed by walking for 1 minute in a 9m corridor at maximum walking speed without running. CYP use normal walking aids and wear orthoses).	Metres	
Participation (restriction)	Involvement in daily activities	Participation and Environment Measure for Children and Youth' (PEM-CY) (Coster et al., 1998)	Parent reported Questionnaire (25 item~ 25 minutes to complete) <i>Answered at home or in clinic</i>	Score	The PEM-CY assesses participation in home, school and community, along with environmental factors within each of these settings Can be completed online at home or in clinic on a handheld device/ paper format whilst waiting for the child's assessment to be completed.
Quality of life	Quality of life across various domains	Cerebral Palsy Quality of life measure (CPQOL) (Davis et al 2013)	CYP(or proxy)reported Questionnaire CP QOL-Child / CP QOL Teen <i>Answered at home or in clinic</i>	Score	The CP QOL-Child designed to assess the quality of life of children aged 4-12 years - parent report for children aged 4 to 12 years and a self-report for children aged 9 to 12 years (52-66 items). CP QOL Teen 13-18 years. Adolescent self-report version and a parent version (72-89 items).
Goal setting (ICF domains)	Selection of goals CYP hopes to improve following BoNT-A	Modified Canadian Occupational Performance Measure (mCOPM) (Law et al., 1998)	In clinic 3 Goals set by CYP and family pre injection Scores assigned post injection	Score (1-10)	mCOPM rates perception and satisfaction of CYP's performance on a 1-10 ordinal scale. A score change of > two points is considered clinically significant

Table 4-2 Study Outcome Measures throughout the ICF

Chapter 5 Results Phase I: Participant demographics and BoNT-A treatment details

This chapter presents the demographics and clinical variables of the children enrolled in the study. Preliminary univariate analyses of the primary outcome measures; The Quality Function Measure (QFM) and Canadian Occupational Performance Measure (COPM) are presented in Chapter 6, with univariate analysis of secondary outcome measures from all domains of the ICF presented in Chapter 7. The results from hierarchical multilevel regression analysis after adjusting for clinical confounders are presented in Chapter 8.

5.1 Sample and Recruitment

The study took place within The Movement Disorder Service at Great Ormond Street Hospital for Children between September 2017 and July 2020. Children referred for BoNT-A treatment in the Botulinum Toxin Service pre-assessment clinic were screened for eligibility to enter the study between September 2017 and July 2019 (Figure 5-1).

During this time 394 children were referred into the service, 105 children potentially met the inclusion criteria. Assessment by the clinical team confirmed eligibility for lower limb BoNT-A, and 70 children were invited to participate by the researcher (LK). Six children declined due to family circumstances and 64 children were recruited and a single group repeated measures study was conducted.

Study recruitment was slower than expected due to a difficulty in recruiting a balanced number of CYPwCP within each GMFCS level. Recruitment was initially planned for 18 months and extended to 22 months to recruit more children into GMFCS level III and during this time more children from GMFCS levels I and II were also recruited.

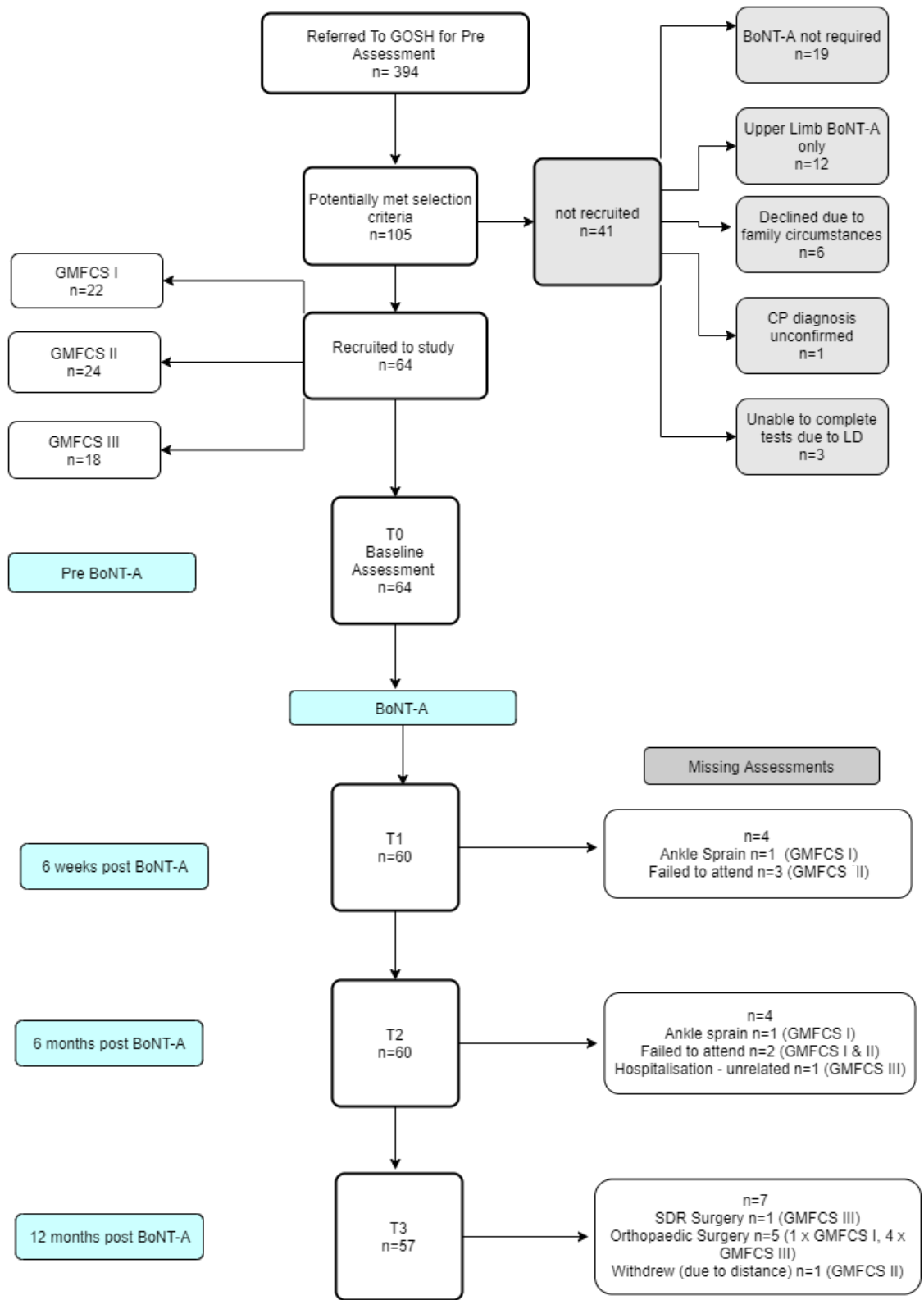


Figure 5-1 Study flow chart according to CONSORT guidelines
SDR= Selective Dorsal Rhizotomy LD= Learning Disabilities

The slow recruitment to the study was unexpected as earlier pilot data had suggested that more children within GMFCS level III (38%) than GMFCS level I (34%) or II (28%) had previously received BoNT-A treatment within the service (unpublished data Katchburian, 2013). This could have been due to a change in service delivery with the introduction of a Selective Dorsal Rhizotomy (SDR) service. SDR is often targeted at children in GMFCS Level III and therefore may have reduced the number of children being referred for BoNT-A.

As shown in Figure 5-1, the study assessment time points were co-ordinated with the four clinical assessment sessions: Pre BoNT-A injections (T0), six weeks (T1), six months (T2) and 12 months (T3) post BoNT-A injections. All 64 children received a baseline assessment (T0) as detailed in Chapter 4 (4.1.4).

At 6 weeks post injection assessment (T1), 60 children (94%) attended, 4 children did not attend; 1 child did not attend due to injury (ankle sprain) and 3 children failed to attend their follow up appointment. Additionally, 2 children were unwell during the assessment and were unable to complete the activity assessments*.

At the 6-month assessment post injection (T2), 60 children completed the assessments (94%). There were missing data for 4 children (these were different children from those missing data at T1); 2 children failed to attend, 1 child had an injury (ankle sprain) and 1 child did not attend due to an inpatient hospital stay.

At the 12-month assessment (T3), 57 children (89%) completed the assessments, with 7 children not attending the final clinical assessment.

- 6 children had surgery between T2 and T3
 - 5 children had orthopaedic surgery (GMFCS Level I n=1, GMFCS Level III n=4)
 - 1 child (GMFCS Level III) had selective dorsal rhizotomy (SDR))
- 1 child (GMFCS Level II) was unable to attend due to problems with the distance travelled (this child had also missed the clinical assessment at T1). When contacted the family did not want to continue treatment at GOSH and

the available data from time point T0 and T2 was used in the descriptive analysis.

50 children (78%) attended assessments at all four time points T0-T3 (GMFCS I n=18, GMFCS II n=20, GMFCS III n= 12) (Figure 5-1). There were complete assessments with all outcome measures for 48 children*.

The attrition rate for this study was 22% and this was mainly due to intermittent attrition. As highlighted above, one child missed two out of the four appointments and thirteen children missed one assessment time point. As this was a repeated measures longitudinal study, descriptive statistics included all the available data at each assessment time point, however, inferential statistical analysis was based on the complete data set available (N=48*: GMFCS level I n=18; Level II n=19; Level III n=11). This sample size of 48 was in keeping with the power calculation of 36 participants.

Participant characteristics and treatment details for the whole sample are summarised in the following sections.

5.2 Demographics

Baseline characteristics for the children enrolled in the study are outlined in Table 5-1

Baseline characteristics of participants	n	%
Female	35	55
Male	29	45
Cerebral Palsy distribution		
Unilateral (Left/Right)	24 (11/13)	37.5
Bilateral	40	62.5
Dominant tone presentation		
Spastic	13	20
Mixed spastic/dystonic	51	80
Gross Motor Function Classification System (GMFCS) Level		
Level I	22	34
Level II	24	38
Level III	18	28
Age (years)		
mean (SD)	7.4 (2.8)	
Range	4-16.8	
Age Strata		
4-8 years	46	71.8
9-18 years	18	28.2
Weight (kg)(SD)	25.8 (10.0)	
range	10-65.9	
Co-morbidities (number of children)	31	48.4
Co-morbidities Details		
Learning Disabilities (Mild/Moderate/severe)	22 (13/8/1)	34.4
Autistic Spectrum Disorder	6	9.4
Epilepsy	3	4.7
Previous BoNT-A injections		
0	19	29.7
1	13	20.3
2	16	25.0
3	5	7.8
4	8	12.5
5	1	1.6
6	1	1.6
7	1	1.6

Table 5-1 Baseline characteristics of participants

The demographics for the participants were in keeping with other research in the field (Delgado et al., 2016b, Read et al., 2017, Yap et al., 2010), with the majority of

the children younger than 9 years of age and 50% receiving injections for the first or second time. Further clinical details of the intervention during the study period are summarised in Table 5-2.

	n (SD)	%
Unilateral/bilateral injections	32/32	50/50
Lower Limb Muscle-groups-injected [unilateral/bilateral] *		
Distal	36 [26/10]*	56.3
Proximal	12 [1/11]*	18.8
Multilevel	16 [6/10]*	25.0
Dose BoNT-A Dysport® (AbobotulinumtoxinA)		
Mean Total Dose (Units)	454 (193)	
Mean Total BoNT-A (Units/kg bodyweight)	18.54 (6.72)	
Additional upper limb injections	12	18.8
Adverse events		
Adverse events (Detail)	11	17.2
Pain/discomfort		
Flu like illness	3	4.7
Localised weakness	1	1.6
Localised weakness+ bladder instability	5	7.8
	2	3.1
Mean time of assessment pre/post BoNT-A (weeks)		
T0	5.30 (3.27)	
T1	7.36 (1.89)	
T2	26.58 (3.96)	
T3	50.79 (2.60)	
Physiotherapy post-injection		
6 week block	63	98.4
4 week block	1	1.6
Serial casts-post injection (number of children)		
Mean time casts worn (weeks)	4	6.3
	3.75 (1)	
Further treatment within study		
Re-injection	24	38
Mean time to reinjection (weeks)	41.3 (4.0)	
Surgery: Orthopaedic/SDR	6 (5/1)	9
Mean time (weeks)	43.3(7.3)/48.2	

Table 5-2 Clinical characteristics of study participants

Key: *Distal muscle groups = injections into muscles inserting below the knee *Proximal Muscle group= injections into muscles inserting above the knee *Multilevel injections = injections to both proximal and distal muscle groups as shown in Figure 4-2

There was an a priori analysis plan was to stratify children into three age groups: 4-8 years, 9-12 years, and 13-18 years. However, since only one child was recruited in the teenage age band (16.8 years, GMFCS Level I), the sample was subsequently re-stratified into only two age groups 4-8 years (71.8%) and 9-18 years (28.2%)

Table 5-1).

This age stratification is in keeping with other work where ‘younger’ age groups are stratified below nine years old (Tilton et al., 2015). The distribution of children as per GMFCS level related to their age is summarised in Figure 5-2

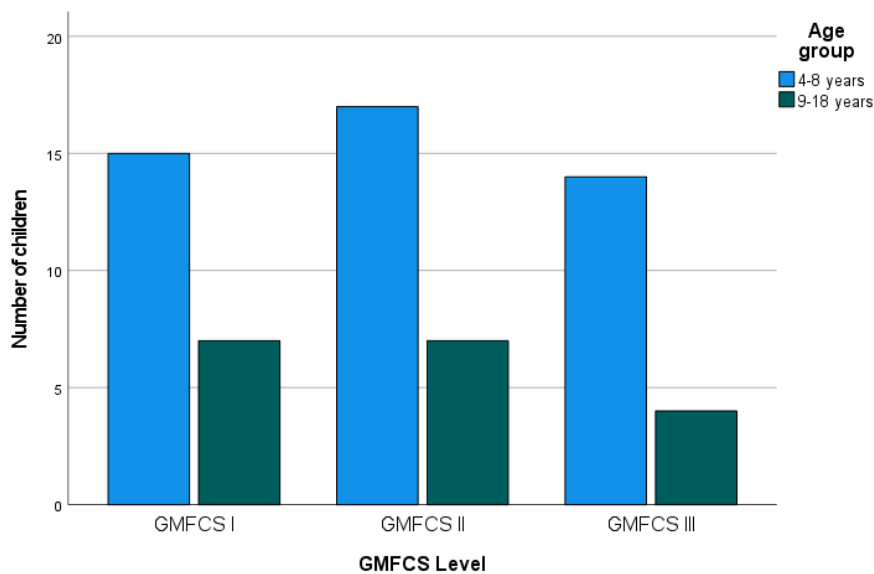


Figure 5-2 Age grouping by GMFCS Level

5.2.1 BoNT-A treatment details of study participants

At enrolment the median number of prior injection cycles for the whole sample was 2.5 (IQR 1,3.75). Nineteen children (29.7%) were classified as ‘toxin naïve’ and received BoNT-A injections for the first time during the study, thirty-four children (53.1%) had received ≤ 3 injection cycles (range 1-3) and eleven children (17.3%) had received ≥ 4 injection cycles (range 4-7) prior to enrolment.

The details of previous BoNT-A injection cycles with GMFCS levels highlighted are summarised in Figure 5-3. The majority of participants (75%) had undergone less

than 3 previous injection episodes and no children in GMFCS II had received more than 4 previous injection episodes.

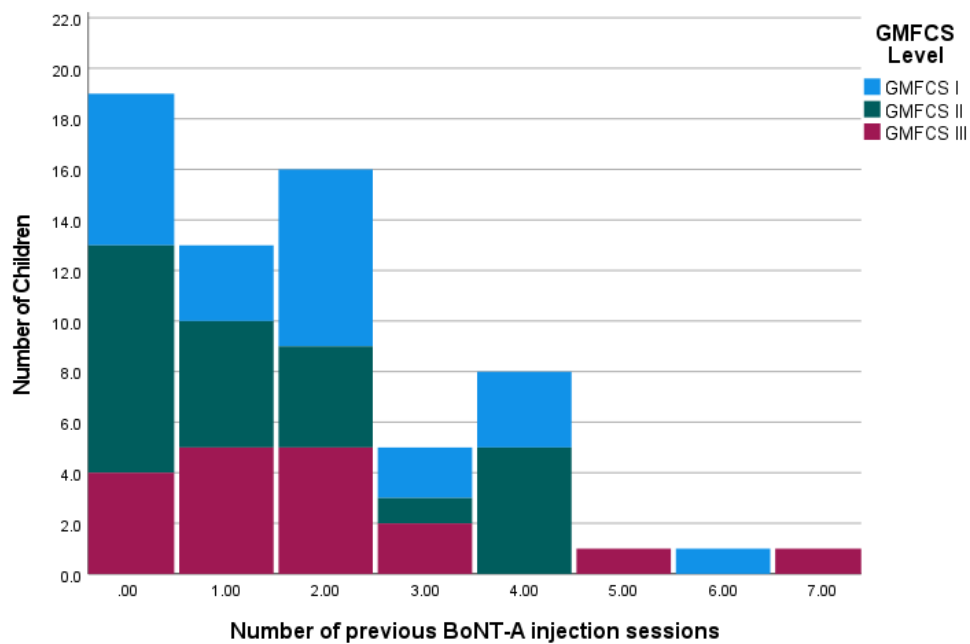


Figure 5-3 Number of previous BoNT-A injection episodes

As this was a pragmatic study reflecting usual clinical practice there was variety in the number of injections each child received. The muscle groups selected were individual to each child’s clinical need and the decision regarding which hypertonic muscles to inject was based on usual practice at GOSH in accordance with clinical expertise and best practice guidelines (Katchburian et al., 2008, NICE, 2012).

Details of the treatment received within the study can be found in Table 5-3. Muscle groups injected were categorised into three groups; ‘*distal*’ muscles that insert below the knee joint, ‘*proximal*’ muscles that insert above the knee joint and ‘*multilevel*’ if both distal and proximal muscles were treated (Figure 4-2). The number of muscles injected varied (range 1-6), with the majority of children (45.3%) having two muscles injected (Table 5-4). As can be seen in Figure 5-4, the most frequently injected muscles were Gastrocnemius in 52 children (81.2%) and Hamstrings in 25 children (39.1%). Table 5-5 shows further detail regarding the muscle groups injected per child.

Hypertonic Muscle groups injected		Total number of children injected <i>n</i> (% of total group)	Bilateral (n)	Unilateral (n) (L/R)	Total number of muscles injected (n)	Mean dose BoNT-A units/kg bodyweight(SD)	Range BoNT-A (units/kg bodyweight)
Gastrocnemius	D	52 (81.2)	21	31 (15/16)	73	9.7 (1.1)	5-10.8
Soleus	D	11 (17.2)	0	11 (6/5)	11	4.9 (0.4)	4.2-5.5
Tibialis Posterior	D	11 (17.2)	0	11 (5/6)	11	5.5 (0.8)	3.9-6.6
Extensor Hallucis Longus	D	1 (1.6)	0	1 (0/1)	1	4.6	
Hamstrings	P	25 (39.1)	18	7 (3/4)	43	6.7 (1.4)	4.8-10.6
Gracilis	P	9 (14.1)	7	2 (1/1)	16	5.4 (0.7)	4.5-6.3
Adductor Longus	P	1 (1.6)	1	0	2	3.9	
Rectus Femoris	P	1 (1.6)	1	0	2	4.2	

Table 5-3 Muscles injected and details of BoNT-A (abobotulinumtoxinA) dose D=Distal muscle groups P=Proximal muscle groups

Number of Muscles injected	1 muscle	2 muscles	3 muscles	4 muscles	5 muscles	6 muscles
Number of Participants <i>n</i> (%)	11 (17.2%)	29 (45.3%)	9 (15.6%)	13 (20.3%)	1 (1.6%)	1 (1.6%)

Table 5-4 Number of muscles injected in one injection episode

Muscle Grouping	Number of muscles injected <i>per limb</i>	Muscles injected	Number of participants	Unilateral/bilateral injections
Distal	1	Gastrocnemius	18	10/8
D	2	Gastrocnemius + Soleus	8	8/0
D	2	Gastrocnemius + Tibialis Posterior	7	5/2
D	3	Gastrocnemius + Tibialis Posterior + Extensor Hallucis longus	1	1/0
D	3	Gastrocnemius + Soleus + Tibialis Posterior	2	2/0
Proximal	1	Gracilis	1	0/1
P	1	Hamstrings	6	1/5
P	3	Hamstrings + Gracilis	3	0/3
P	3	Hamstrings + Gracilis + Adductor Longus	1	0/1
P	2	Hamstrings + Rectus Femoris	1	0/1
Multilevel	2	Hamstrings + Gastrocnemius	10	3/7
M	3	Hamstrings + Gastrocnemius + Gracilis	2	1/1
M	3	Hamstrings + Gastrocnemius + Soleus	1	1/0
M	3	Hamstrings + Gastrocnemius + Tibialis Posterior	1	1/0
M	2	Gastrocnemius + Gracilis	2	0/2

Table 5-5 Combination of muscle groups injected during the study per participant

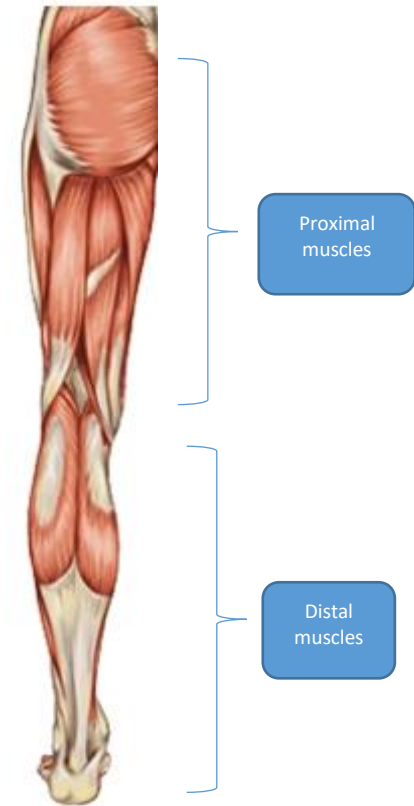
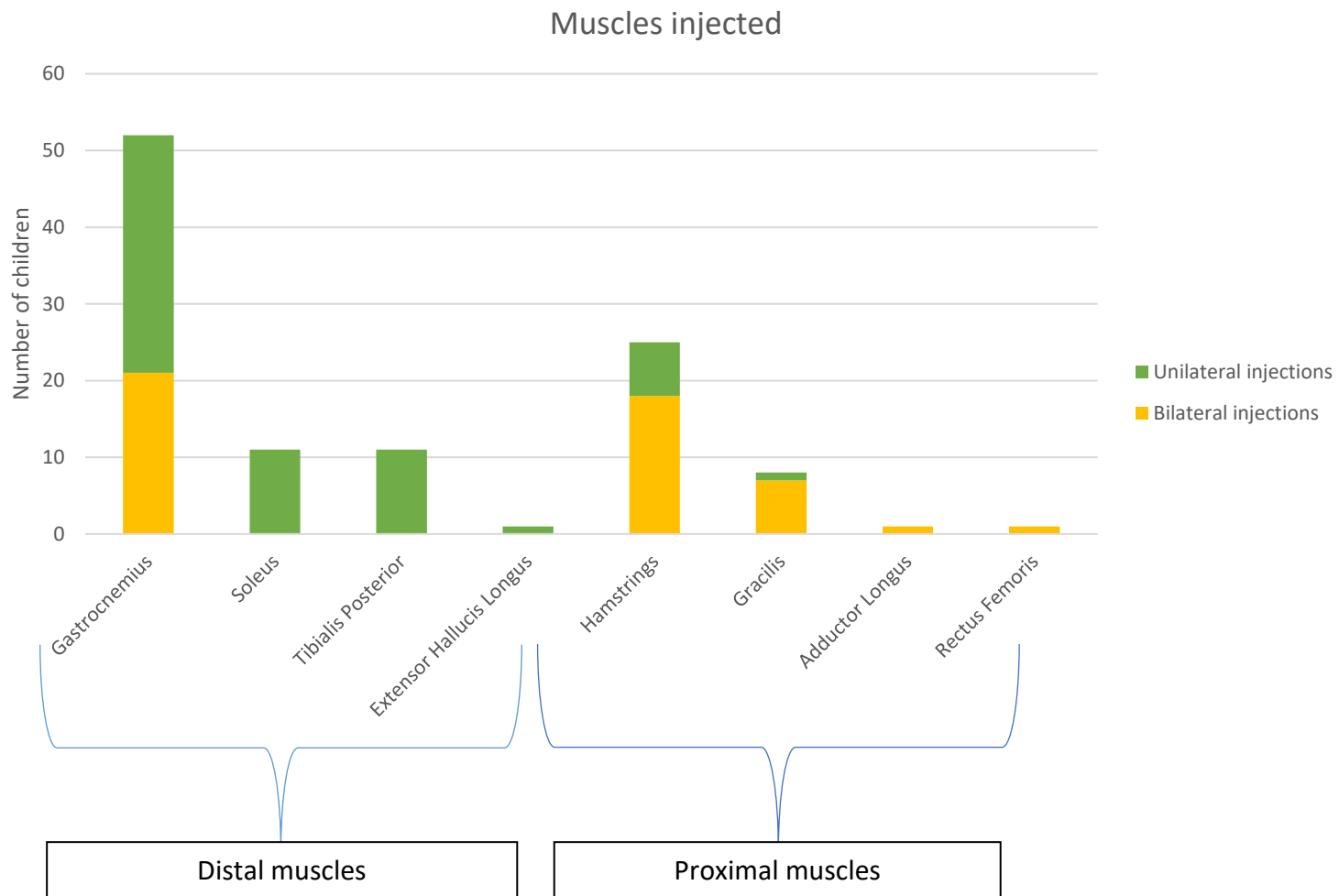


Figure 5-4 Muscles injected in the study

A variation was observed in the site of injections when examined by GMFCS level for the group, 86.4% of children in GMFCS Level I and 58.3% in GMFCS Level II received injections into distal muscle groups, whereas children in GMFCS level III were more likely to receive injections into proximal muscle groups (44.4%) or multilevel injections (38.9%) levels as highlighted in Figure 5-5.

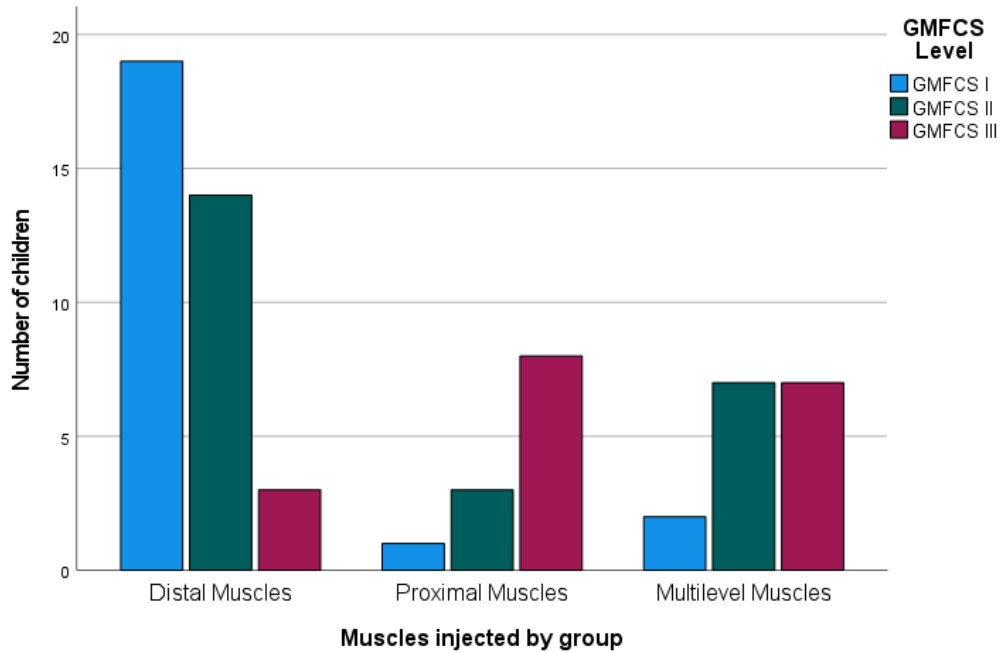


Figure 5-5 Muscle groups injected within GMFCS Levels

The detail regarding the number of treatment cycles children had prior to entering the study have been summarised in Figure 5-6. As expected, there was a difference in the number of previous injection cycles related to age group, with only 3 children (6.5%) in the younger age group having more than 4 previous injection cycles in comparison to 8 (44.4%) children in the older age group.

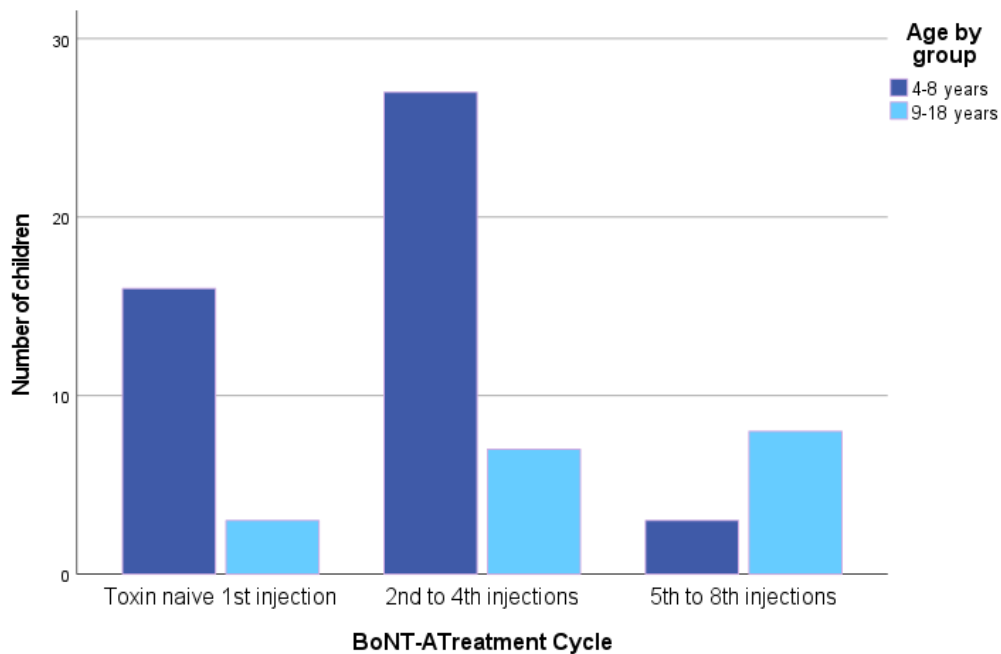


Figure 5-6 Treatment session as related to age groups

Within the study all children received a period of physiotherapy rehabilitation post injection, 63 children (93.8%) received weekly physiotherapy sessions for six-weeks and one child for four weeks (due to an ankle injury). Therapy was provided in the community setting by the child’s usual provider and the content of the therapy sessions was left to the discretion of the local physiotherapist. All local therapists were aware of the goals set by the family prior to injection. Therapists treating children in the study identified programmes tailored to the individual child. These included targeting functional strengthening, flexibility, balance, core stability and functional goal directed activities including gait training.

Adverse events following BoNT-A injections were reported in 11 children (17.2%). All of these were considered mild and transient and were commonly reported side effects following treatment with BoNT-A (Paget et al., 2018b). All had resolved by T1 assessment (details of adverse events are summarised in Table 5-2).

5.2.2 Treatment received within the study

All 64 children enrolled in the study received a single injection episode between T0 and T2. As this was a pragmatic clinical study, further treatment options were available following clinical assessment at T2 before children were assessed at T3 (see 4.1).

Between T2 and T3, six children (9.4 %) underwent surgery; five children had orthopaedic surgery (mean time to surgery 43.3 weeks SD=7.9 post injection) and one child had selective dorsal rhizotomy (48.2 weeks post injection). These children were not re-assessed at T3.

Following assessment by the clinical team, 24 children (37.5%), received a further injection episode between T2 and T3 (mean time to re-injection 41.3 weeks SD=4.0 post original injection) and 34 children (53.1%) did not require a further injection episode within the study period. All 58 children were invited for assessment at twelve months (T3).

Children were reviewed at T3 following re-injection with mean time to follow up of 9.4 weeks post second injection episode (SD=2.3 weeks). Re-injection within the study was included as a confounding variable during multilevel regression modelling to account for any differences in outcome between children with a single injection cycle over 12 months and those children who had two injection episodes.

5.3 Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 27.0 for Windows (IBM Corp, 2020) and R Statistical Software (R Core Team, 2021, RStudio Team, 2021). All statistical tests were performed with a significance set at 0.05, with significant values further explored by post hoc testing using a Bonferroni correction to minimise type I error. All graphs show error bars representing 95% confidence intervals.

A test of normality was conducted for all outcomes using the Shapiro -Wilk test, together with visual inspection of their histograms. Not all outcomes were normally distributed as shown by non-significant test scores (see Appendix 14.1 for Shapiro-Wilk tests for all outcome measures). However as the sample size was more than 30 (n=64) and non-normality is said not to substantially affect Type I error rate, continuous data were analysed using the parametric one-way repeated measures ANOVA test which is said to be robust to deviations from normality (Laerd Statistics, 2015).

All outcomes were initially explored using univariate analysis to compare changes at three time points post BoNT-A treatment T1-T3 (6 weeks, 6 months and 12 months post injection) in comparison to baseline scores (Chapter 6 primary outcome measures and Chapter 7 secondary outcomes).

Multilevel regression analysis of the data was then conducted in order to adjust for clinical confounders in this pragmatic study, and a linear multilevel regression model was fitted to account for the effect of BoNT-A treatment with time on the outcomes in the study (AKAIKE, 1979, Bliese P, 2016, Kuznetsova et al., 2017). The results of the multilevel modelling are summarised in Chapter 8, with the repeated measurements of each individual defining the level element of the multilevel model.

In order to ensure consistency between the details of each analysis, results and discussion, descriptive statistics consisting of means and standard deviations have been provided for all outcome variables. Parametric descriptors have been used throughout where possible to ensure uniformity and enable comparison with the results from multilevel modelling in Chapter 8.

Additionally, descriptive statistics are summarised in the Appendix 14.8.1 using medians and IQR with non-parametric tests to evaluate repeated measures. Similar results were obtained for both parametric and non-parametric tests.

Missing data

As this was a longitudinal study using repeated measures for all outcomes, inferential statistical analysis was based on the complete data set available (N=48: GMFCS level I n=18; Level II n=19; Level III n=11).

There were no statistically significant differences between the missing data sets and those of the complete data sets for any primary or secondary activity and participation outcomes (Mann Whitney U tests to determine differences in outcomes between the two data sets $p > .05$ can be found in Appendix 14.8.2).

Chapter 6 Results Phase I: Primary outcome measures

This chapter presents the results from the two primary outcome measures used within the study QFM and COPM

6.1 Quality Function Measure (QFM)

The use of the QFM to evaluate change in Quality of Movement (QoM) in this study was novel within the field of interventions for CYPwCP. Minimal detectable difference estimates for each of the QFM attributes had been published by the test developers (Table 6-1) which indicated that the QFM might be acceptable for evaluative purposes, however there was no published work establishing responsiveness to change following an intervention such as BoNT-A.

This chapter presents details of descriptive and univariate analysis of the QFM to evaluate the effect of BoNT-A injections on QoM over a twelve-month period. This is followed by details of QFM administration including scoring time, intra-rater reliability and minimal detectable difference for each attribute. Finally, correlations between each of the attributes are explored for the cohort of participants in this study.

QFM was scored from video recordings of the Gross Motor Function Measure (GMFM) recorded by the clinical team at baseline, pre- injection (T0) and at the post injection assessments (T1-T3). Items from dimensions D and E of the GMFM were used to score quality of movement to provide the five individual QFM attribute scores:

- Alignment
- Co-ordination
- Dissociated Movement
- Stability
- Weight shift

The mean time to perform the GMFM assessment during the clinical appointment was 37 mins (range 25-60 minutes), children were encouraged to continue through the test items according to individual ability. Children in GMFCS levels I and II were able to complete more GMFM items due to their greater motor ability than children in GMFCS Level III. Children with GMFCS level III completed fewer test items but took longer to complete the tests. Clinicians observed increasing fatigue in children of GMFCS level III when asked to perform repeated trials of each of the items that they were able to do in Dimensions D and E. The mean time to complete the test differed between GMFCS levels and was also influenced by motor planning ability; GMFCS Level I=27.5 mins (SD 8.8 mins), Level II=35 mins (SD 6.1 mins), Level III= 48.8 mins (SD 7.4 mins).

Although QFM item scores are usually based on an average of three trials, to reduce test burden and fatigue during the clinical assessment, only two trials were typically performed in this study. This was pertinent for children in GMFCS level III who had greater difficulty carrying out the test and particularly repeating the items three times. The number of trials was discussed with the test developers, who confirmed that reliability estimates for individual QFM attribute scores were equivalent whether two or three trials were performed (personal correspondence, Wright 2017).

Video data were recorded from 239 completed GMFM Dimension D and E sessions.

- 64 children at baseline, pre-injection (T0)
- 58 children (90.1%) at 6 weeks post-injection (T1),
(Although 60 children attended T1 assessment, one child was unwell during the assessment and one child had a broken arm, so both were unable to complete the GMFM test)
- 60 children (93.8%) at T2
- 57 children (89.0%) at T3.

6.1.1 QFM Analysis

Changes in each of the five QFM attributes were analysed individually. These results were related to both statistical significance and published minimal detectable change (MDC) values. The MDC (also referred to as minimum detectable difference MDD) has been defined as the smallest amount of change that can be detected not due to inherent variation (also described as ‘noise’) in the measure with a change in outcome exceeding MDC values suggesting that an intervention programme is effective (Chen et al., 2012, Villalba et al., 2021)

QFM test developers identified what they describe as *conservative* minimal detectable change values (MDC) values for each of the attribute scores with 80 % and 90% confidence intervals (MDC₈₀, MDC₉₀) for GMFCS Levels I-III (Wright et al., 2014a). These values are summarised in Table 6-1 and can be used to evaluate the magnitude of change in order to assess meaningful clinical change in the absence of published MCID studies and represent an approximation of medium (MDC₈₀) and large (MDC₉₀) effect sizes (personal communication Wright 2021).

QFM	MDC ₈₀ (%)	MDC ₉₀ (%)
Alignment	13.5	17.4
Co-ordination	8.7	11.2
Dissociated movement	8.4	10.8
Stability	9.9	12.7
Weight shift	8.4	10.8

Table 6-1 MDC Scores for QFM

MDC values are clinically useful for evaluating meaningful change, particularly following interventions. For example, if children score $\geq 9.9\%$ change on the QFM Stability attribute, a clinician can be 80% confident that the CYPwCP has shown true improvement, likewise if children score $\geq 12.7\%$ change, clinicians can be 90% confident that the CYPwCP has shown true improvement (Chen et al., 2012).

6.1.2 QFM Descriptive Analysis

The mean scores and standard deviations of QFM scores for the total sample are summarised in Table 6-2. There was an increase in all QFM attribute scores post BoNT-A injections in comparison to baseline pre-injection scores (Figure 6-1).

	Baseline T0 n=64	6 weeks T1 n=58	6 months T2 n=60	12 months T3 n=57
Mean(SD) %				
Alignment	52.7 (25.4)	69.4 (23.8)	68.3 (24.5)	70.3 (23.1)
Co-ordination	58.3 (27.7)	67.2 (28.9)	69.8 (28.2)	69.4 (28.2)
Dissociated movement	46.6(22.1)	54.7 (25.4)	55.9 (23.9)	56 (24.5)
Stability	53.4 (28.3)	62.3 (29.7)	64.3 (28.6)	64.9 (29.0)
Weight shift	51.8 (21.5)	60.64 (23.2)	61.9 (22.2)	63.1 (22.5)

Table 6-2 Mean QFM percentage scores for the total sample

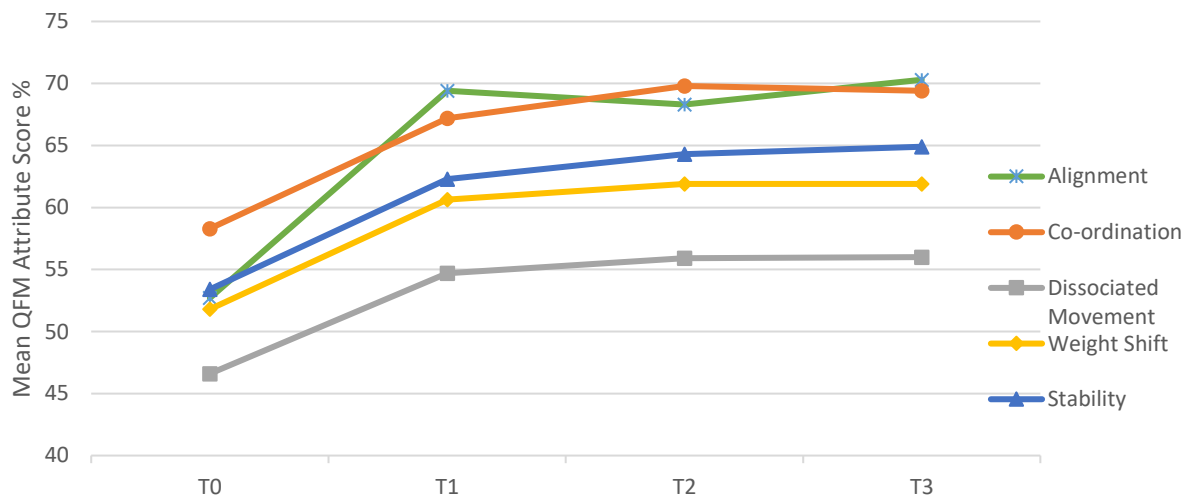


Figure 6-1 Mean QFM Attribute Scores across all time points

This graph shows significant improvement from baseline scores in all five attributes over 12 months ($p < .001$)

Further examination of QFM mean scores relative to GMFCS levels showed a difference in scores at all time points across all QFM attributes between GMFCS

levels. Individual GMFCS level scores have been summarised in Table 6-3, showing higher QFM scores with increased motor ability.

QFM % scores [Mean(SD)] GMFCS I/II/III	T0 n=22/24/18	T1 n=21/20/17	T2 n=20/23/17	T3 n=21/23/13
Alignment				
GMFCS I	67.7 (19.3)	82.4 (17.2)	81.0 (16.5)	86.4 (10.8)
GMFCS II	60.6 (18.5)	75.7 (14.5)	75.7 (14.3)	75.3 (18.7)
GMFCS III	21.1 (14.0)	35.7 (16.7)	32.1 (16.4)	42.4 (16.7)
Co-ordination				
GMFCS I	77.4 (16.7)	85.5 (15.3)	87.5 (12.2)	87.8 (11.3)
GMFCS II	66.3 (18.1)	76.3 (17.1)	77.6 (16.0)	80.7 (14.1)
GMFCS III	22.9 (14.3)	25.9 (13.2)	26.7 (11.2)	27.4 (12.9)
Dissociated movement				
GMFCS I	63.1 (12.4)	71.4 (14.9)	72.1 (12.4)	73.1 (13.8)
GMFCS II	51.3 (13.4)	61.6 (15.9)	62.1 (12.7)	64.3(14.9)
GMFCS III	17.9 (10.9)	19.3 (10.4)	20.0 (9.7)	23.0 (11.4)
Stability				
GMFCS I	72.8 (16.9)	80.8 (15.5)	81.9 (11.9)	83.0 (11.3)
GMFCS II	62.0 (19.1)	71.8 (16.6)	72.9 (15.7)	76.7 (16.2)
GMFCS III	17.1 (15.4)	19.5 (14.8)	18.9 (11.1)	22.5 (13.9)
Weight shift				
GMFCS I	65.9 (14.4)	74.1 (15.2)	75.2 (11.9)	77.3 (12.9)
GMFCS II	58.5 (14.4)	68.3 (13.6)	67.7 (12.8)	70.9 (12.7)
GMFCS III	24.8 (11.3)	28.1 (10.6)	28.3 (8.9)	31.8 (10.5)

Table 6-3 Mean QFM scores by GMFCS level

As expected, QFM scores were highest for GMFCS level I and lowest in GMFCS Level III for all QFM attributes. This is in keeping with Wright et al. (2014a) who demonstrated similar mean values in their discriminant validity analysis, and established that the QFM was able to discriminate across all levels ($p < .001$) for all attribute comparisons at a single assessment time point. However, in the absence of published MDCs for individual GMFCS Levels it is difficult to interpret the absolute significance of change scores within each level.

The difference in scores between GMFCS Levels is illustrated in Figure 6-2 which shows the strong correlation between QFM attributes at baseline ($0.88 < r < 0.98$) and also demonstrates the discriminative ability of QFM to pick up differences between GMFCS levels. There is a consistently higher score associated with GMFCS level I (blue) for all attributes, with GMFCS Level II (green) scores lower but higher than GMFCS Level III (red) scores.

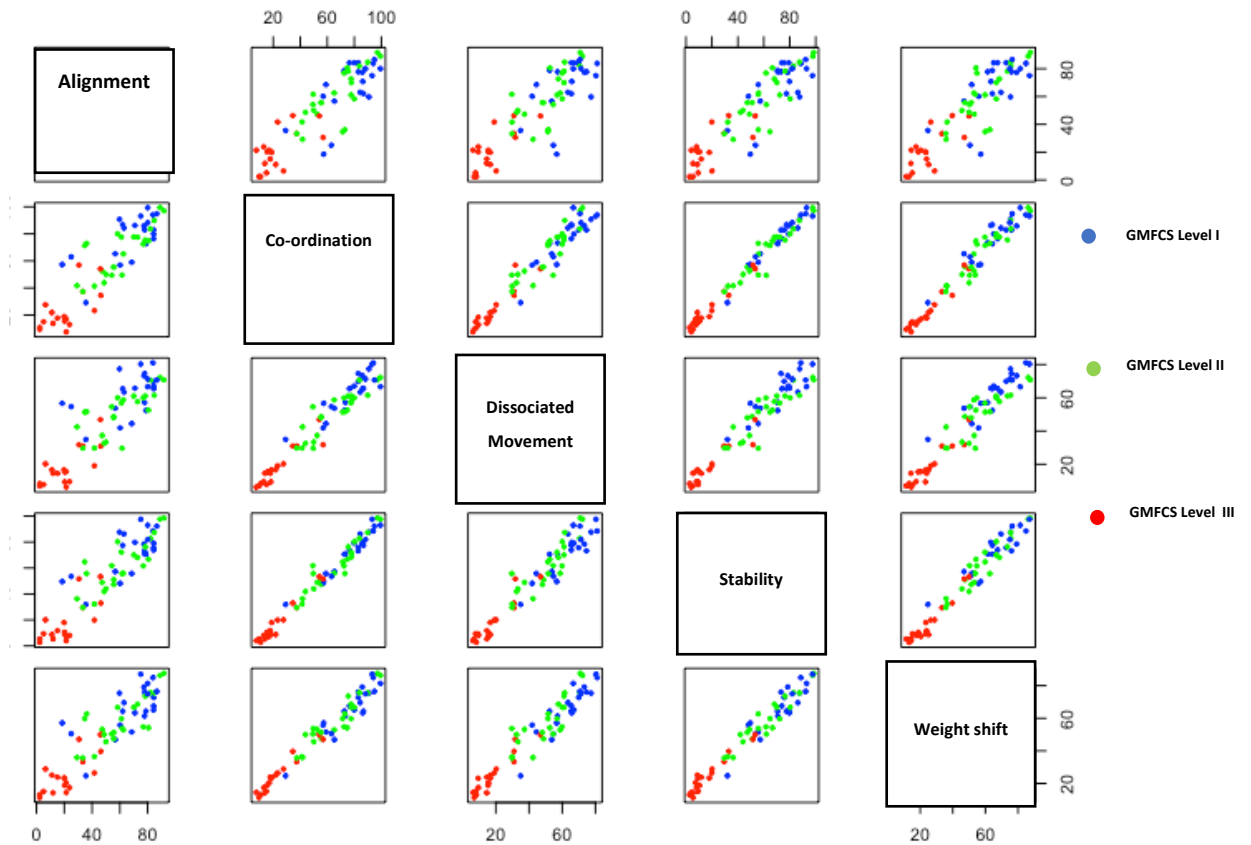


Figure 6-2 Scatter plot showing Baseline correlations of QFM attributes highlighting GMFCS levels ($0.88 < r < 0.98$)

Further analysis of correlation data for post-injection time points is shown later in this chapter together with discussion of the psychometric properties of the QFM (6.1.5).

6.1.3 QFM Univariate analysis

A one-way repeated measures ANOVA was conducted to evaluate change in QFM scores over the twelve months. The main effect of time was significant across all QFM attributes, showing a statistically significant difference in scores across the four time points (T0-T3). The results for all five QFM attributes are summarised in Table 6-4 and suggest a large effect size as suggested by the Partial Eta Squared values (η_p^2) across all QFM attributes (Cohen, 2013)

The assumption of sphericity as assumed by Mauchly's test was not met in the case of three QFM attributes (co-ordination, stability, and weight shift), so a repeated measures ANOVA with a Greenhouse-Geisser correction was applied.

n=48	F (3,141)	p-value	Partial Eta Squared η_p^2	Mauchly's test of Sphericity
Alignment	63.74	<0.001	0.58	0.058
Co-ordination*	63.44	<0.001	0.57	<0.001
Dissociated movement	36.41	<0.001	0.44	0.345
Stability*	52.73	<0.001	0.53	<0.001
Weight shift*	71.22	<0.001	0.60	0.023
* Greenhouse-Geisser correction				

Table 6-4 One way repeated measures ANOVA for QFM attributes (effect of Time)

Boxplots for all QFM attributes (Figure 6-3) revealed an improvement in percentage scores from baseline at all three post injection time points for each of the five QFM attributes.

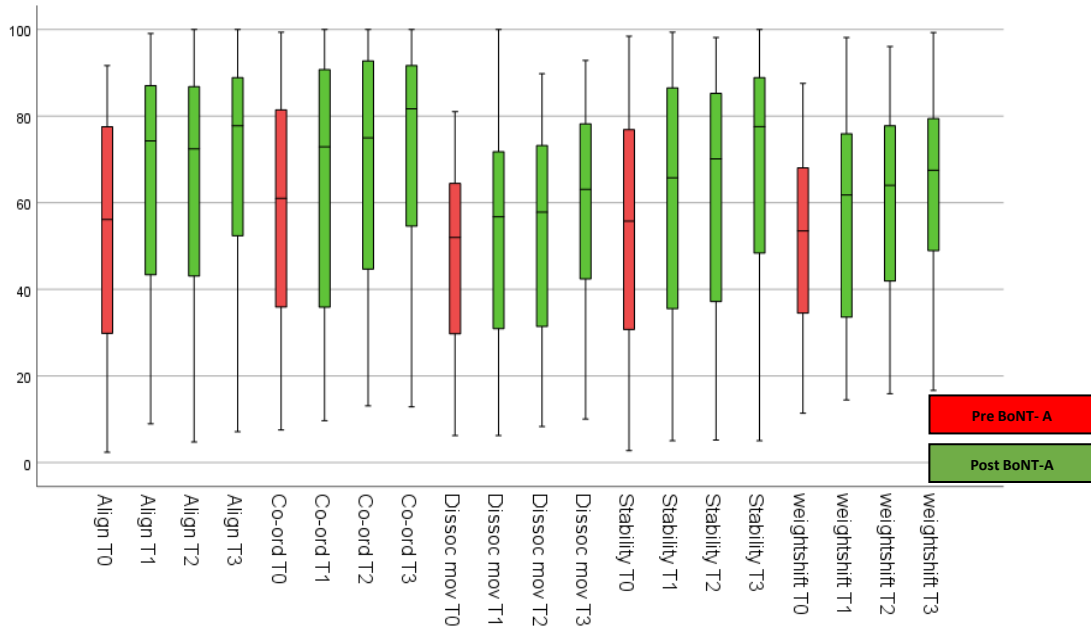


Figure 6-3 Box Plot of mean % QFM attribute scores at all time points N=48

The QFM findings for all attributes are summarised in Table 6-5 and are compared to the published minimal detectable change (MDC) values (Wright et al., 2014a).

Mean difference QFM Attribute	Change Score from baseline (%) (95% Confidence interval)			
	n = 48	T1	T2	T3
Alignment		16.7 ^a (12.8,20.7)	15.9 ^a (11.3, 20)	17.6 ^b (12.6,22.6)
Co-ordination		9 ^a (6.2,11.6)	12 ^b (8.5,14.5)	11 ^b (7.9,14.3)
Dissociated movement		8.1 (4.7,11.5)	9.3 ^a (6.4,12.2)	9.4 ^a (6.4,12.3)
Stability		8.9 (5.9,12)	10.8 ^a (7.5,14.2)	11.4 ^a (7.8,15.0)
Weight shift		8.9 ^a (6.4,11.3)	10.1 ^a (7.4,12.8)	11.3 ^b (8.5,14.1)

a ≥MDC80 b ≥MDC90 all results significant p<.001

Table 6-5 Mean Change score QFM attributes from baseline scores

The univariate results for QFM attributes suggested a clinically significant improvement in Alignment, Co-ordination, and Weight shift at 6 weeks post injection and in all attributes at 6- and 12-months post injection.

6.1.4 QFM Attribute scores

Individual attribute scores are presented in the following sections to evaluate change from baseline scores following BoNT-A injections. Additional analysis regarding differences related to GMFCS level or number of injection cycles within the study is also shown. Each section has a definition of the attribute from the test developers (wright et al., 2014b) and a brief clinical summary highlighting what an improvement in score would mean for a child with CP.

6.1.4.1 Alignment

‘The adjustment or arrangement of parts or segments of the body in relation to each other’

Improved alignment can be seen when a child’s limb positioning has less malalignment and more symmetrical movement is seen in the limb.

Mean Alignment scores increased from baseline (pre- injection) to all three post BoNT-A assessment time points (Figure 6-1). One-way repeated measures ANOVA indicated that there were statistically significant changes in Alignment scores ($p<.001$) over time following BoNT-A injections (Table 6-4).

Post hoc analysis with a Bonferroni adjustment revealed that mean alignment scores were statistically significantly increased ($p<.001$) at all post injection time points in comparison to baseline (Table 6-5). Changes at T1 and T2 exceeded the published MDC₈₀ (moderate effect size) value of 13.5% and exceeded MDC₉₀ (large effect size) value of 17.4% at T3 suggesting clinical significance in addition to statistical significance at all post injection time points.

Results for GMFCS level and re-injection status within the study period (occurring between T2 and T3) were analysed further. Children within all GMFCS levels showed an improvement in alignment scores in comparison to baseline pre-injection scores. As anticipated there was a difference in QFM alignment scores between the different GMFCS levels (Table 6-3), children in GMFCS III consistently scored lower

in comparison to children in both GMFCS levels I and II ($p < 0.001$) (Figure 6-4). The lower alignment scores in GMFCS level III children were to be expected reflecting a lower level of motor ability and capacity to carry out the items in the GMFM-66 on which the QFM is based. Although the mean alignment scores for children in GMFCS level II were lower than those children in GMFCS I, this difference between the two levels was not statistically significant ($p = .10$).

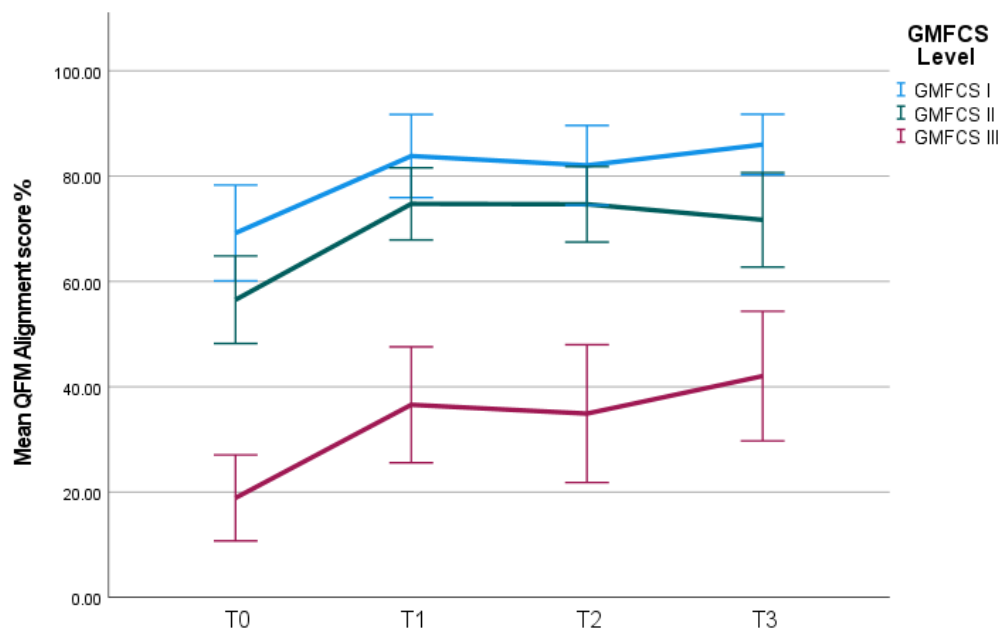


Figure 6-4 QFM Alignment scores by GMFCS Levels (n=48).
 Children in GMFCS III scored lower than children in GMFCS levels I and II ($p < 0.001$). The difference in scores between children in GMFCS I and II were not statistically significant ($p = .10$)

Analysis of alignment scores by re-injection within the study is shown in Figure 6-5. Although mean Alignment scores reduced 6 months post injection (T2) for children who were selected for reinjection following this assessment, post hoc analysis with a Bonferroni adjustment revealed no statistically significant difference in alignment scores between children who received a second injection cycle within the study and those children who received a single injection cycle ($p = .92$).

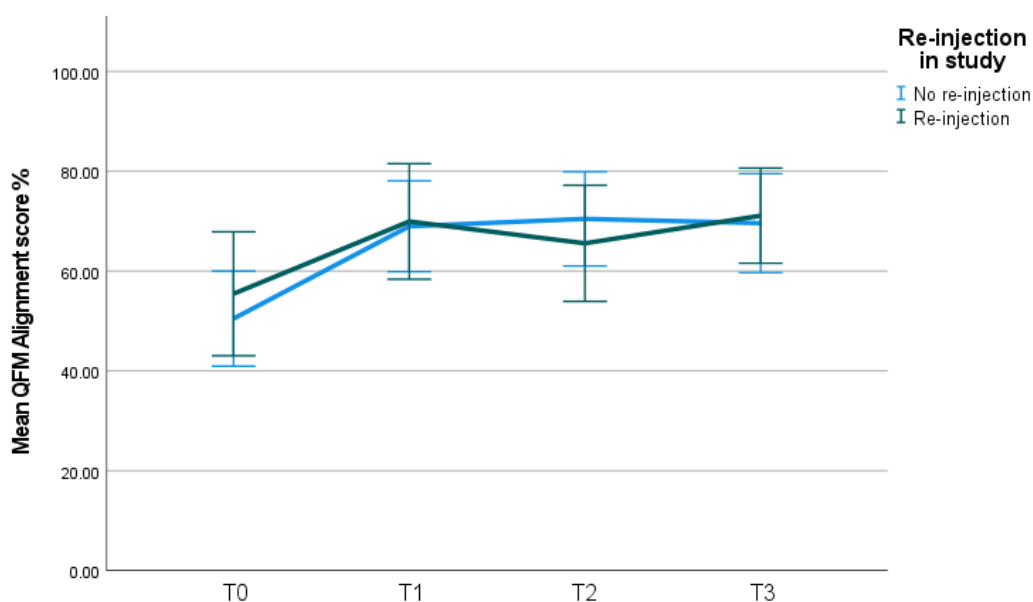


Figure 6-5 QFM Alignment scores by reinjection within the study (n=48)
 The difference between the two groups was not statistically significant (p=.92)

6.1.4.2 Co-ordination

'The smooth and controlled use of movements in motor performance'

Improved co-ordination can be seen when a child's movement sequencing and motor planning are improved. Movements may appear 'smoother' and more fluid and controlled.

As shown in Figure 6-1, mean Co-ordination scores improved from baseline at 6 weeks, 6 months, and 12 months. One-way repeated measures ANOVA indicated that there were statistically significant changes in Co-ordination scores ($p < .001$) over time following BoNT-A injections (Table 6-4).

Post hoc analysis with a Bonferroni adjustment revealed that co-ordination was significantly improved ($p < .001$) at all post injection time points in comparison to baseline scores. Changes at T1 exceeded MDC_{80} (8.7 %), suggesting a clinically significant improvement with a moderate effect size. At T2 and T3 these exceeded the published MDC_{90} value of 11.2% suggesting a clinically significant improvement

with a large effect size. in addition to statistical significance post injection at all time points following BoNT-A treatment (Table 6-5)

GMFCS level and re-injection results within the study period for Co-ordination were analysed between T2 and T3. As expected, there was a difference in QFM scores between GMFCS levels reflecting a child's level of dependence and motor ability (Table 6-3). Once again, these scores were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) but co-ordination scores were also significantly higher for children in GMFCS Level I in comparison to those in Level II ($p = .047$).

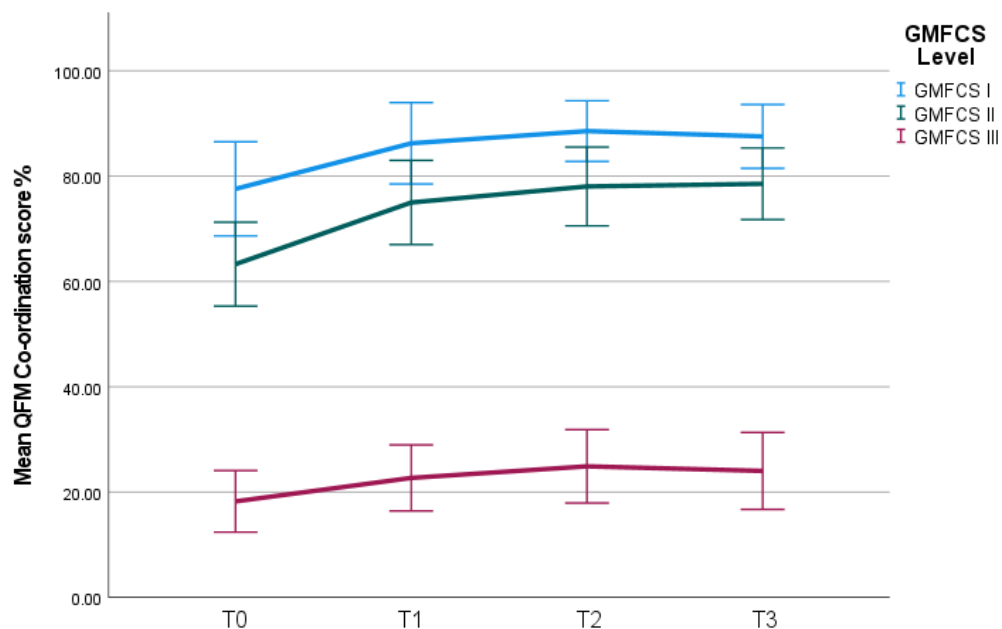


Figure 6-6 QFM Co-ordination Scores by GMFCS Level

Co-ordination scores were significantly lower for children in GMFCS III in comparison to those in GMFCS I and II ($p < .001$) but children in GMFCS I also scored significantly higher than those in Level II ($p = .047$).

Co-ordination scores were lower for children who required re-injection compared with those who did not require re-injection during the study but as with alignment scores this difference was not statistically significant ($p = .34$) (Figure 6-7)

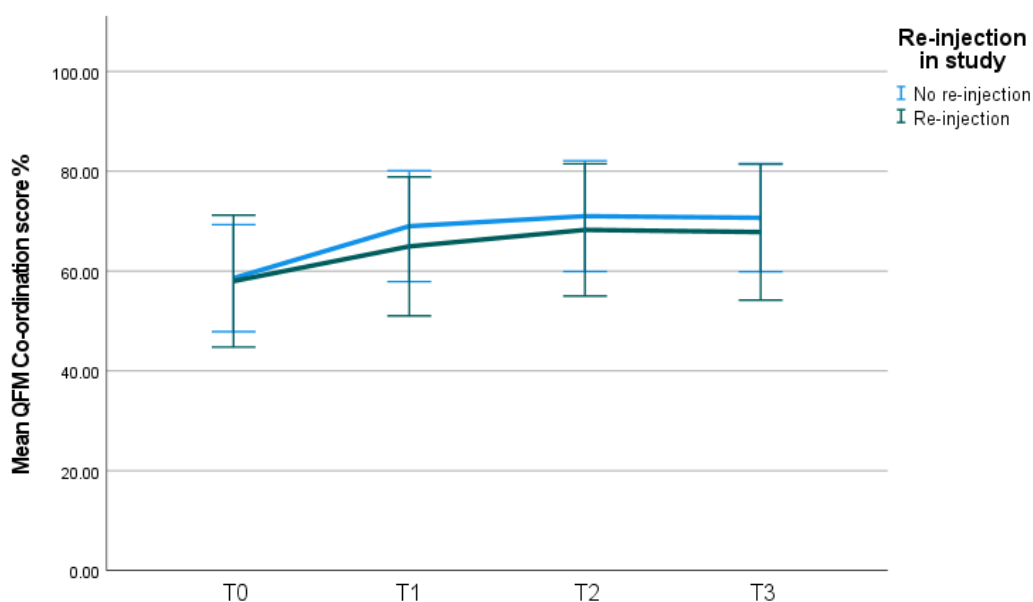


Figure 6-7 QFM Co-ordination Scores by reinjection within the study.
 There was no significant difference in scores between the two groups (re-injected and single injection in the study) at any time point ($p=.34$)

6.1.4.3 Dissociated Movement

‘Movement of one segment of the body independent from another segment’

Improvement in Dissociated Movement is seen when a child is able to move each limb or joint in isolation and is usually a measure of reduced stiffness.

As can be seen in Figure 6-1, Quality of movement as assessed by Dissociated Movement scores were significantly improved from baseline pre-injection scores at 6 weeks and further improved at both 6 and 12 months.

One-way repeated measures ANOVA results demonstrated statistically significant changes in Dissociated Movement scores over time ($p<.001$) following BoNT-A injections (Table 6-4).

Post hoc analysis with a Bonferroni adjustment revealed that Dissociated Movement scores were significantly increased at all post injection time points ($p < .001$). However, when these were compared to published MDC values, only changes at T2 and T3 reached clinical significance and exceeded the published MDC_{80} value of 8.4% (Table 6-5)

Once again, the results for Dissociated Movement were analysed by GMFCS level and re-injection within the study period (between T2 and T3). As expected, there was a difference in QFM scores between GMFCS levels reflecting a child's motor ability (Table 6-3). These scores were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) as in previous attributes but as with co-ordination scores, there was also a significant difference in Dissociated Movement scores between GMFCS Levels I and II ($p = .009$), with GMFCS level I children demonstrating a significantly higher level of dissociated movement reflecting their improved motor ability (Figure 6-8).

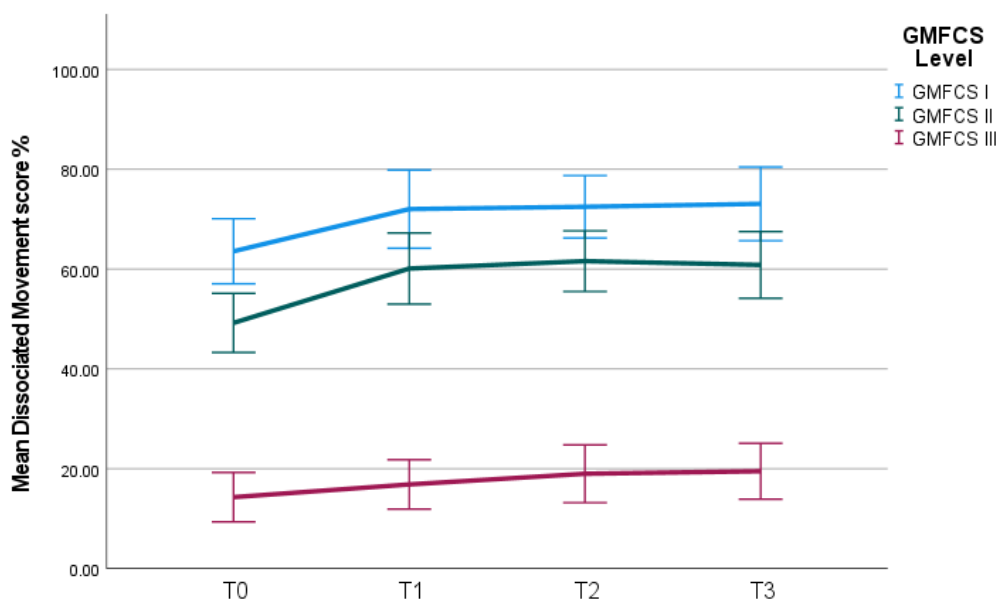


Figure 6-8 QFM Dissociated Movement Scores by GMFCS Levels.

Scores were significantly lower for children in GMFCS III than children in GMFCS Levels I and II ($p < .001$). There was also a significant difference in Dissociated Movement scores between GMFCS Levels I and II ($p = .009$)

In keeping with other QFM attributes there were no differences in Dissociated Movement scores ($p=.40$) between children who had re-injection within the study and those who had a single injection cycle (Figure 6-9).

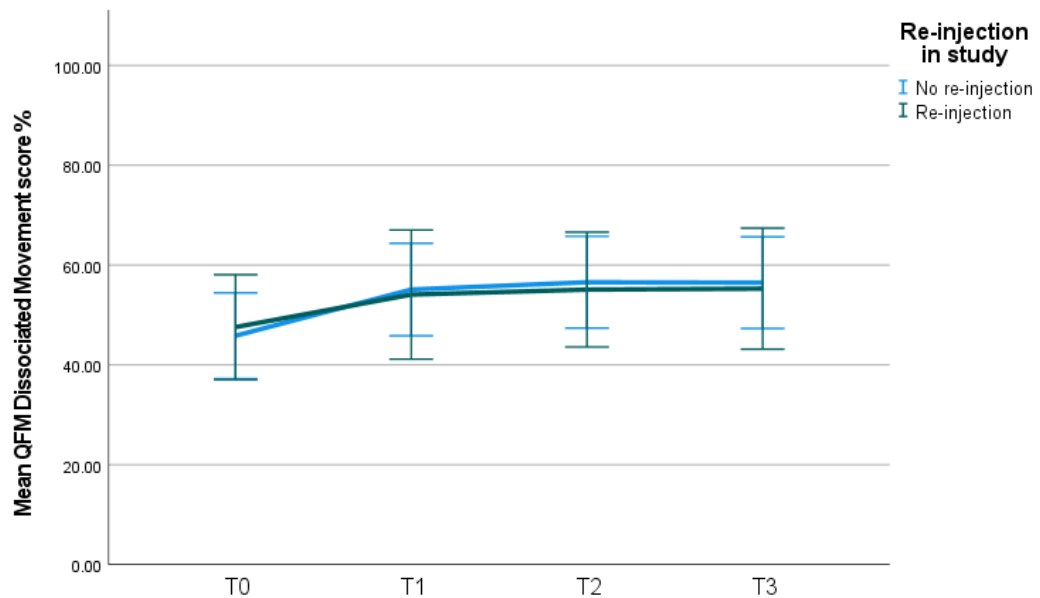


Figure 6-9 QFM Dissociated Movement score by re-injection within the study.
 There was no significant in scores between the two groups (re-injected and single injection in the study) at any time point ($p=.40$)

Stability

‘The active maintenance of a body position in the presence of disturbing forces’

Improved stability is usually reflected in a child’s improved balance in both static and dynamic activities, and this can result in reduced trips and falls.

QFM Stability scores significantly improved at 6 weeks post injection in comparison to baseline scores (Figure 6-1) and continued to show further improvement in comparison to baseline at 6 months which was maintained at 12 months (Table 6-2). A one-way repeated measures ANOVA results indicated statistically significant changes in Stability scores ($p<.001$) over time following BoNT-A injections (Table 6-4).

Post hoc analysis with a Bonferroni adjustment revealed that Stability significantly increased at all post injection time points ($p < .001$). Changes at time point T1 did not reach clinical significance. However, at T2 and T3 changes exceeded the published minimal important clinical difference MDC_{80} value of 9.9% suggesting clinical significance with moderate effect size in addition to statistical significance at 6 and 12 months (Table 6-5)

Further analysis of Stability scores was again carried out by GMFCS level and re-injection status between T2 and T3. As with earlier QFM attributes there was a difference between QFM scores between GMFCS levels reflecting a child's motor ability (Figure 6-10). These scores were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) but unlike Dissociated Movement or Co-ordination were not significantly different between GMFCS Levels I and II ($p = .052$).

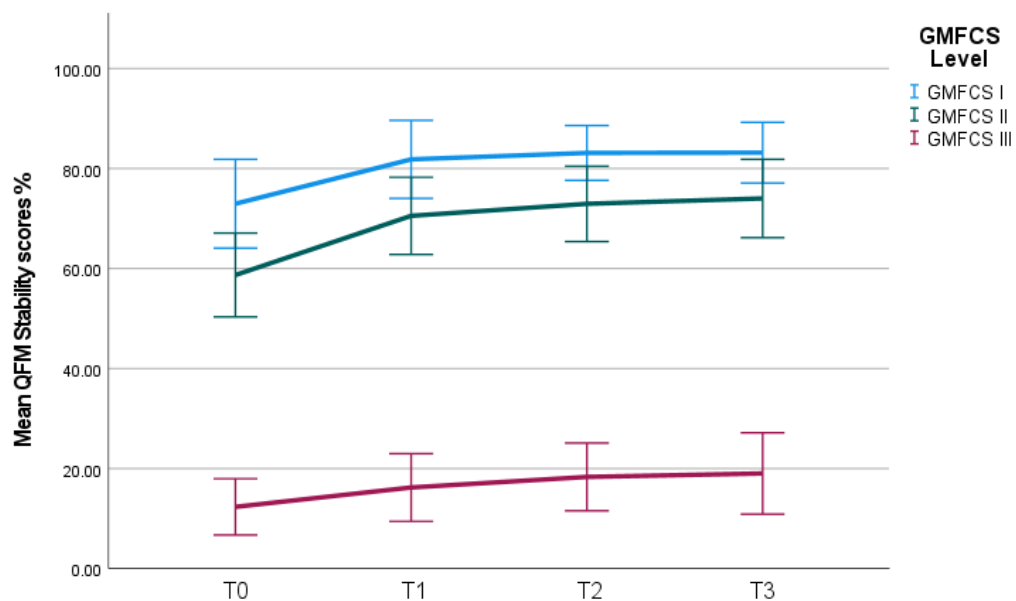


Figure 6-10 QFM Stability Scores by GMFCS Levels.

These scores were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) but not significantly different between GMFCS Levels I and II ($p = .052$).

There were no significant differences in Stability scores ($p=0.24$) observed between children who had re-injection within the study and those who had a single injection cycle (Figure 6-11)

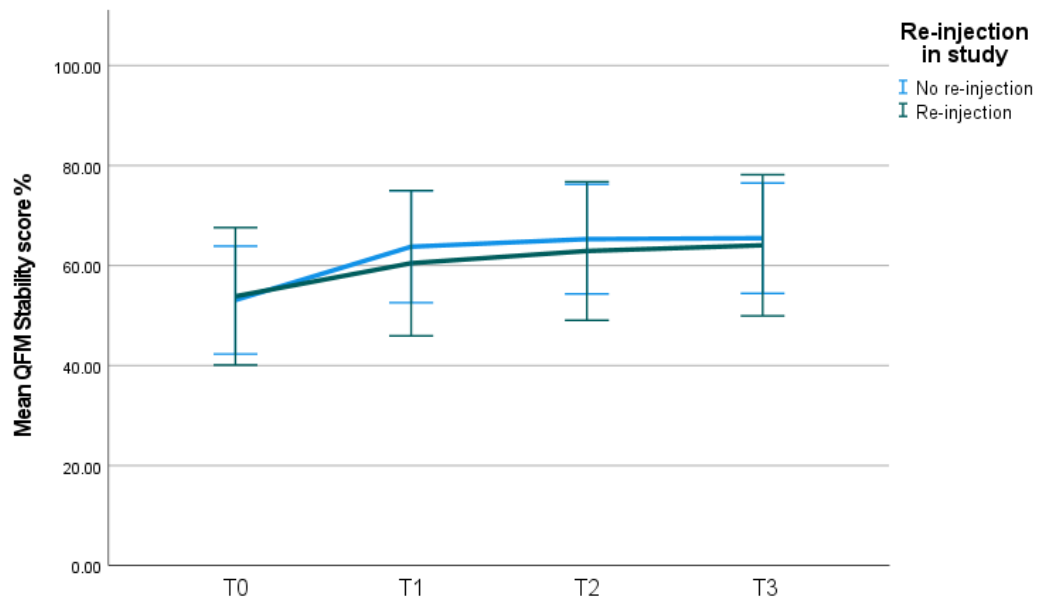


Figure 6-11 QFM Stability Scores by re-injection in the study.

The scores were not significantly difference between the two groups(re-injected and single injection in the study) at any time point ($p=.24$)

Weight shift

‘Movement that involves a transfer of the body’s centre of gravity’

Improvement in weight shift allows a child to transfer body weight more easily to free a limb when performing dynamic movements, this is usually reflected by improved balance and ease of movement.

Quality of movement as assessed by a change in Weight shift scores followed a similar pattern following BoNT-A injection to the other QFM attributes. QFM Weight shift scores significantly improved at 6 weeks post injection in comparison to baseline scores (Figure 6-1) and continued to show further improvement in

comparison to baseline at 6 months which was maintained at 12 months (Table 6-2).

A one-way repeated measures ANOVA indicated significant changes in Weight shift scores ($p < .001$) over time following BoNT-A injections (Table 6-4). Post hoc analysis with a Bonferroni adjustment revealed that Weight shift scores were significantly increased at all post injection time points ($p < .001$). Changes at time point T1 and T2 suggested a clinical significance with a moderate effect size (exceeding MDC_{80} 8.4%) and a large effect size at T3 (exceeding MDC_{90} 10.8 %) suggesting clinical significance in addition to statistical significance at all time points (Table 6-5).

Weight shift results analysed by GMFCS level and re-injection within the study period (between T2 and T3) followed a similar pattern to other QFM attributes. There was a difference between QFM scores within GMFCS levels which reflected a child's motor ability (Figure 6-12). These scores once again were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) but not between GMFCS Levels I and II ($p = .093$).

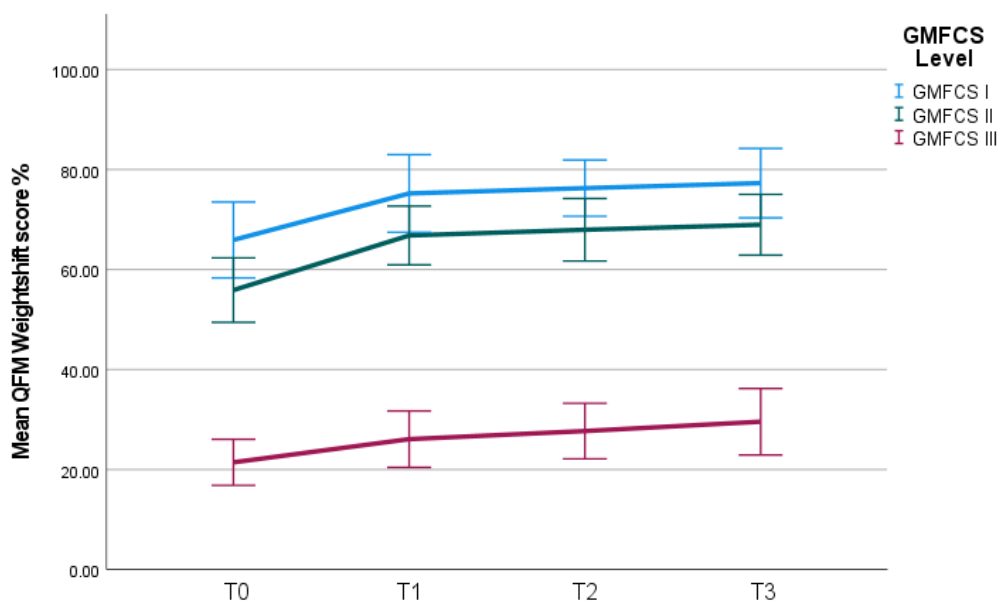


Figure 6-12 QFM Weight shift Scores by GMFCS Levels.

These scores were statistically significantly different between GMFCS Levels I and III and II and III ($p < .001$) but not between GMFCS Levels I and II ($p = .093$).

There were no statistically significant differences in Weight shift scores between children who had re-injection within the study and those who had a single cycle ($p=.12$) (Figure 6-13).

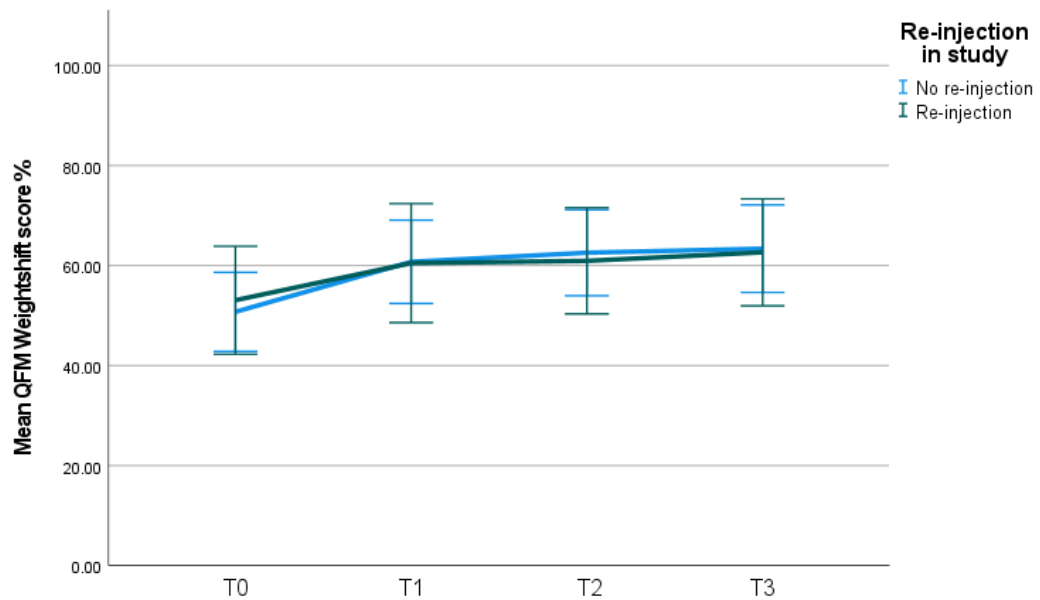


Figure 6-13 QFM Weight shift Scores by re-injection in the study.
 The scores were not significantly difference between the two groups(re-injected and single injection in the study) at any time point ($p=.12$)

6.1.5 QFM Administration

QFM is a novel outcome measure introduced in 2016 as the first standardised validated measure to evaluate QoM in ambulant CYPwCP. However, previous authors have highlighted that administration of the measure, including scoring time, may be excessive for use in the clinical field (Tustin et al., 2016, Wright, 2016).

Administration details including scoring time for this study together with intra-rater reliability and Standard Error of Measurement (SEM), Minimal Detectable Change (MDC) and retrospective power calculation are summarised in the following sections to further inform the psychometric properties of the measure.

6.1.5.1 Scoring time

The 239 videos were scored by the researcher (LK) who was blinded to the intervention time point until all the video clips had been scored for each child in the study. (Full administration details are provided in 4.1.1). The mean time to score the QFM from all 239 videos was 46.78 minutes (SD=11.43) with a minimum time of 15 minutes and a maximum time of 90 minutes. This did not include the preparation and labelling of video items before scoring nor the time to enter the scores in the excel data base developed by the test developers which added a further 20 minutes administration time per video.

The scoring time for the sample as a whole together with individual details of scoring duration for the different GMFCS Levels I, II and III are summarised in Table 6-6.

Number of QFM videos	Whole Sample N=239	GMFCS Level I n=84	GMFCS Level II n=90	GMFCS Level III n=65
Mean minutes (SD)	46.78 (11.43)	45.56 (10.61)	46.89 (11.19)	48.13 (13.13)
Median minutes (IQR)	44.75 (38.94,54.38)	45.13 (38.75,53.63)	44.25 (38.94,51.00)	46.92 (38.38,46.92)
Min-Max minutes	15- 90	25-90	24-75	15-79

Table 6-6 QFM Scoring time (minutes)

There was no significant difference in scoring duration between the four assessment time points ($p=0.74$) nor between the different GMFCS Levels ($p=0.803$). This is an interesting administrative detail for clinical practice, although children in GMFCS Level III were able to complete fewer items due to their reduced motor ability, post-test scoring took as long as for those children in GMFCS I and II who were able to attempt all test items. This was in part due to excess video footage, as children took time to transition between positions and attempt the items, as well as being slower to perform the items.

6.1.5.2 Intra-rater reliability

Intra-rater reliability was established for the study. There was an average of 33.5 days (range 28-36 days, SD 5.2) between the first and second assessments for the 12 videos in the intra-rater study component performed by the researcher (LK).

As shown in Table 6-7 intra-rater ICC estimates were excellent for all attributes, with the lower confidence interval limit exceeding ≥ 0.96 for all attributes. The small SEM values provide further support for the intra-rater reliability of the QFM and are in keeping with the published data (Tustin et al., 2016, Wright et al., 2014a).

Reliability	ICC (2.1)	95%CI	SEM	MDC ₉₅
Mean(SD) %				
Alignment	0.99*	0.98-0.99	1.48	4.11
Co-ordination	0.99*	0.98-0.99	1.95	5.41
Dissociated movement	0.99*	0.99-1.00	2.74	7.61
Stability	0.99*	0.98-1.00	2.90	8.03
Weight shift	0.99*	0.96-1.00	2.23	6.32

SEM=standard error of measurement MDC=minimum detectable change; *p<.001

Table 6-7 QFM Intra-rater reliability statistics

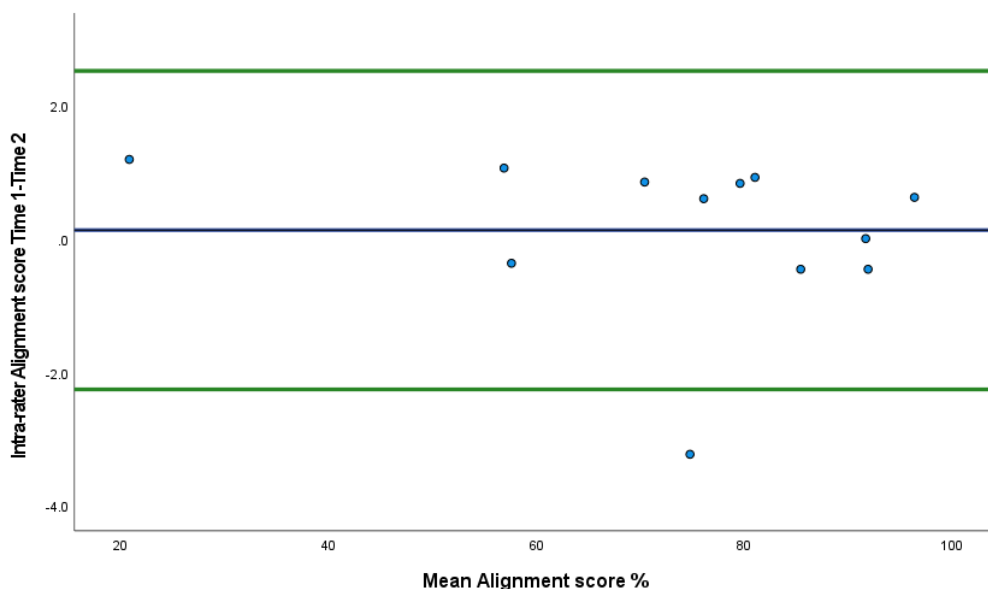
The MDC calculated for this sample based on intra-rater reliability was lower than previously published data by the test developers which ranged from 9 to 17 % (Table 6-1) (Wright et al., 2014a). However the published MDC values for the QFM were based on inter-rater reliability data, whilst the intra-rater values reported by Wright et al. (2014a) in their study were more in keeping with this study's MDC values and are similar to those reported by Tustin et al. (2016).

These results support the views of the QFM developers who suggest that true MDC scores may be lower than the published values (personal communication, Wright 2021). Within this study, the small SEM could also be explained through familiarity with the test as the researcher analysed a large number of QFM videos (239 +12).

Concordance between the sets of measurements produced by different ratings for the same participant was evaluated using Bland-Altman test values. Paired-sample t-tests found no significant difference between intra-rater QFM attribute summary scores.

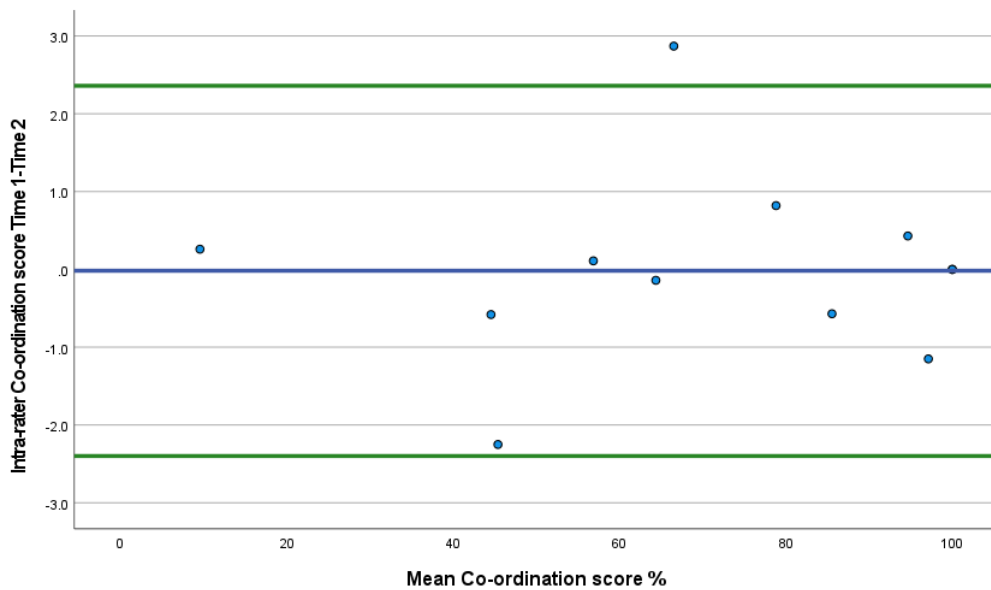
Test results showed close agreement between both ratings as shown in Bland-Altman plots for QFM Alignment (Figure 6-14) and Co-ordination (Figure 6-15). Test values and plots for all QFM attributes can be found in Appendix 14.8.2.

Inspection of the plots suggested no obvious relationship between measurement error and the measured value. The agreement between ratings was very good, with only one of the 60 data points (1.7%) falling outside the limits of agreement (LOA). Despite the small sample size, the LOA was narrow and did not exceed +/- 6 % for any QFM attribute. Risk of proportional bias was assumed to be low as illustrated by linear regression (B coefficients for QFM attributes ranged from -0.01-0.02, $p > 0.05$). The narrow LOAs together with MDC_{95} values for this study suggest that change in scores above 8% for QFM attributes in this study could be considered a meaningful change which was in excess of measurement error.



Green Lines = 95% Limits of Agreement representing +/- 2 SD **Blue line**=Mean difference

Figure 6-14 Bland Altman Plot representing intra-rater agreement for QFM Alignment scores



Green Lines = 95% Limits of Agreement representing +/- 2 SD **Blue line**=Mean difference

Figure 6-15 Bland Altman Plot representing intra-rater agreement for QFM Alignment scores

6.1.5.3 Correlation between Attribute scores

Pearson’s correlation matrices revealed that results between the five QFM attributes were highly correlated at all assessment time points T0-T3 ($| r | > .8$ (Cohen, 2013).

The following pages show examples of scatterplot matrices for correlations between QFM attributes at two time points; 6 weeks (T1) and 6 months (T2) post BoNT-A injections (see Appendix 14.8.4 for similar results for all time points). GMFCS levels are highlighted within the scatterplot matrices illustrating differing scores related to motor ability at all time points.

At all assessment time points, children in GMFCS level I (blue dots) generally scored higher than those in GMFCS Level II (green dots) who scored higher than children in GMFCS level III (red dots).

The high correlation between attributes at T1 (6 weeks post BoNT-A) is shown by the scatterplot in Figure 6-16

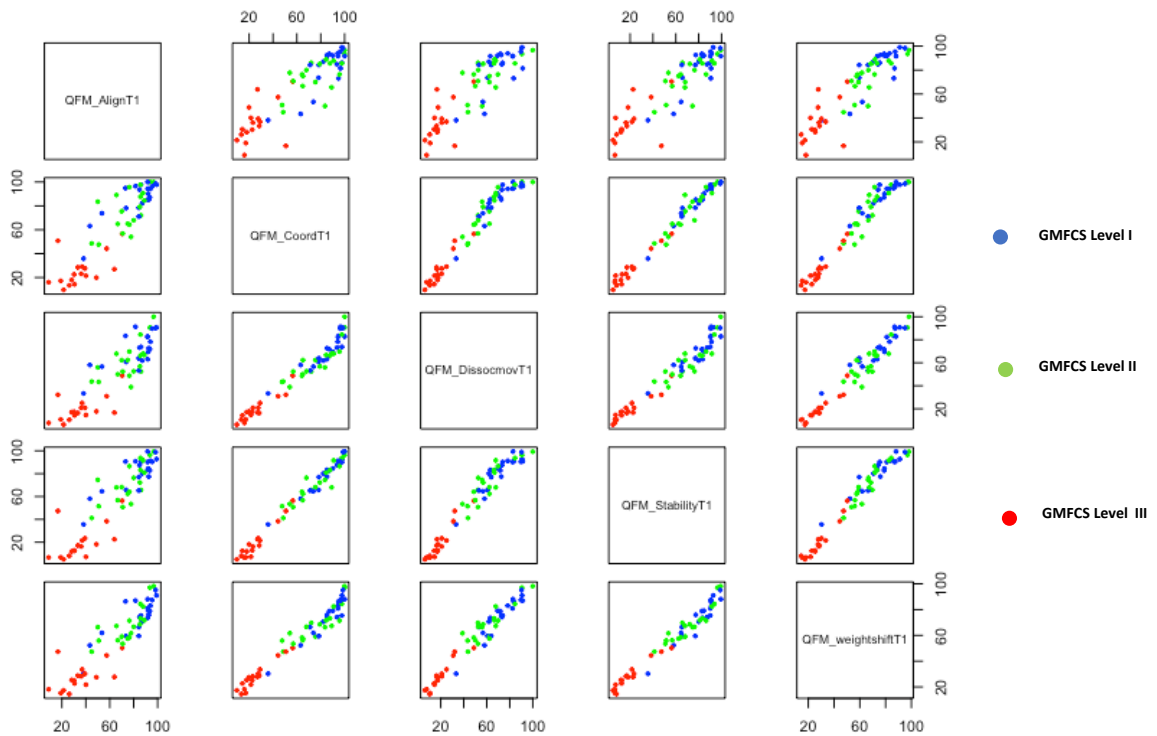


Figure 6-16 Scatter plot matrices showing correlation of QFM attributes at 6 weeks post BoNT-A

QFM T1 Correlation coefficients (95% Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Co-ordination	0.88 (0.81-0.93)			
Dissociated Movement	0.88 (0.8-0.92)	0.97 (0.95-0.98)		
Stability	0.90 (0.84-0.94)	0.99 (0.98-0.99)	0.97 (0.95-0.98)	
Weight shift	0.90 (0.84-0.94)	0.97 (0.96-0.98)	0.97 (0.95-0.98)	0.98 (0.97-0.99)

Table 6-8 Pearson correlation for QFM attribute scores at 6 weeks post BoNT-A

The high correlation between attributes at T2 (6 months post BoNT-A) is shown by the scatterplot in Figure 6-17

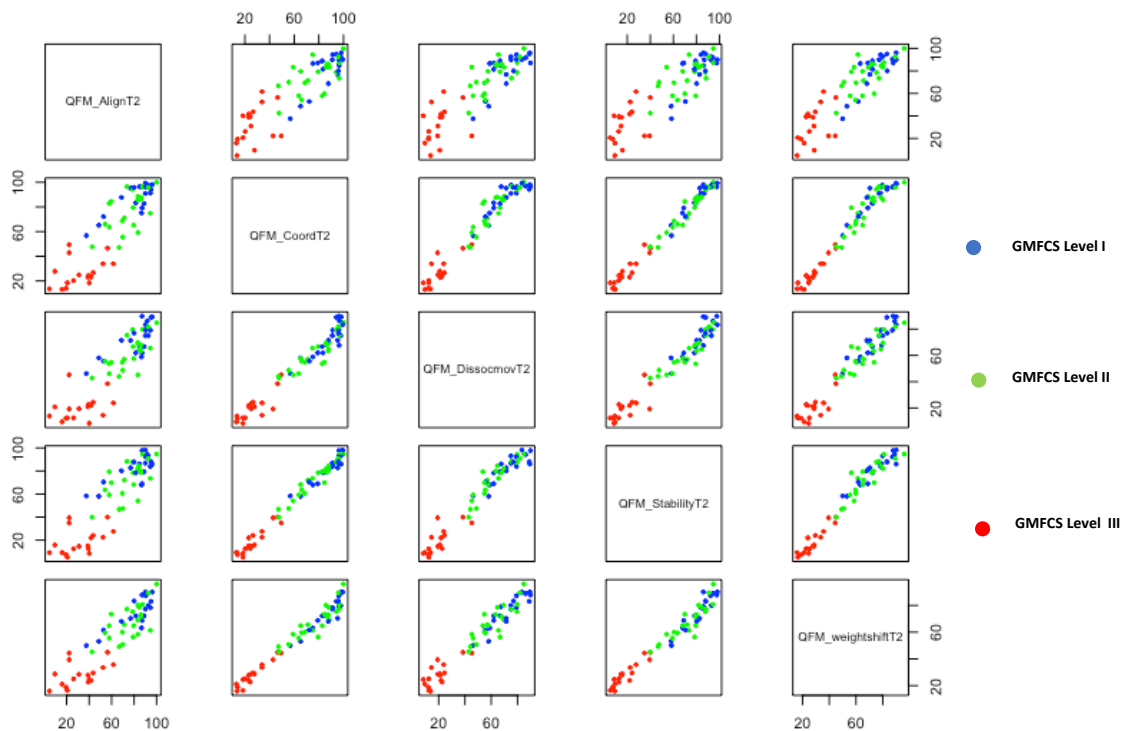


Figure 6-17 Scatter plot matrices showing correlation of QFM attributes at 6 months post BoNT-A

QFM T2 Correlation coefficients (Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Co-ordination	0.88 (0.81-0.93)			
Dissociated Movement	0.88 (0.81-0.93)	0.97 (0.95-0.98)		
Stability	0.88 (0.81-0.93)	0.99 (0.98-0.99)	0.97 (0.95-0.98)	
Weight shift	0.89 (0.83-0.94)	0.98 (0.97-0.99)	0.97 (0.95-0.98)	0.98 (0.96-0.99)

Table 6-9 Pearson correlation for QFM attribute scores at 6 months post BoNT-A

As can be seen in Table 6-8 and Table 6-9 all QFM attributes were highly positively correlated at all time points ($|r| > .8$ (Cohen, 2013)). This is in keeping with previous QFM studies (Tustin et al., 2016, Wright, 2016) and raises the question whether scoring of all QFM attributes is required when evaluating interventions with CYPwCP. This is particularly pertinent in view of the lengthy time for scoring (Table 6-6) which may preclude its acceptability for use in clinical practice.

6.1.5.4 Retrospective power calculation

The retrospective power calculation shown in Table 6-10 focused on the five QFM attributes alignment, coordination, dissociated movement, stability and weight shift for change between baseline and 6 months. The paired test was chosen as the main analysis tool to explore the differences between baseline and 6 month data for the numerical scores of QFM attributes. These values were based on educated estimates from the existing published literature (Tustin et al., 2016, Wright et al., 2014a). A moderate correlation of 0.5 was used between the two time points, with significance levels set at 0.05.

Retrospective Power calculation	Alignment	Coordination	Dissociated Movement	Stability	Weight shift
Mean at baseline	52	58	46	53	51
SD at baseline	25	27	22	28	21
Mean at 6 months	68	69	55	64	63
SD at 6 months	24	28	23	28	22
Significance level	0.05	0.05	0.05	0.05	0.05
Total sample size	64	64	64	64	64
Power (n=64)	99.9%	88.2%	88.2%	87.1%	99.2%
Complete data sample size	48	48	48	48	48
Power (n=48)	99.3%	77.4%	77.4%	75.9%	96.5%

Table 6-10 Power calculation for QFM attributes

As can be seen in Table 6-10 the study appeared to be adequately powered for each of the QFM attributes both with the original sample size of 64 participants and for the 48 complete data sets accounting for attrition due to missed data collection points.

6.2 Canadian Occupational Performance Measure Analyses

The second primary outcome measure for the study was the Canadian Occupational Performance Measure (COPM), the goal attainment tool used in current clinical care at GOSH. COPM identifies concerns regarding ‘occupational performance’ i.e. the ability for a child to carry out functional tasks and, as such, was used to document change post BoNT-A rehabilitation (O’Neil et al., 2003). As per usual clinical practice at GOSH, areas of concern in a child’s self-care, activity and leisure were explored with the clinical team during the baseline assessment prior to receiving BoNT-A injections. Children and families were encouraged to identify three goals for treatment that they would like to attain following lower limb BoNT-A injections (details regarding goal setting can be found in 4.2.1).

The number of goals set varied from child to child with all 64 children identifying at least one goal and four children (6.3%) identifying four goals; however, the majority of children (59.4%) identified three goals. These were then categorised into appropriate ICF-CY domains by the researcher (LK) and classified as either: body structures and functions (BSF), activities and participation (A&P), or environmental factors (Environment) according to the International Classification of Functioning, Disability and Health: Children and Youth Version (ICF-CY) (WHO, 2007). Classification was undertaken in collaboration with the clinical advisory group in order to ensure standardised classification (see Appendix 14.6 for details regarding goals set).

A total of 169 goals were identified by the 64 children in the study with 57.4% of these being identified as activity and participation goals (Figure 6-18). The most frequently chosen goals for children and families focused on walking (53%), with specific goals concentrating on improving gait pattern and reducing trips and falls. Children also selected specific goals around recreation and leisure activities such as swimming, ballet, horse-riding, cycling and karate.

Each set goal was personal and framed to fit in with a child’s everyday life with participation goals ranging from “*keeping heel in a stirrup during riding lessons*” to

“balancing on one leg for 10 seconds in karate” and “being able to wear sliders when walking on the beach”.

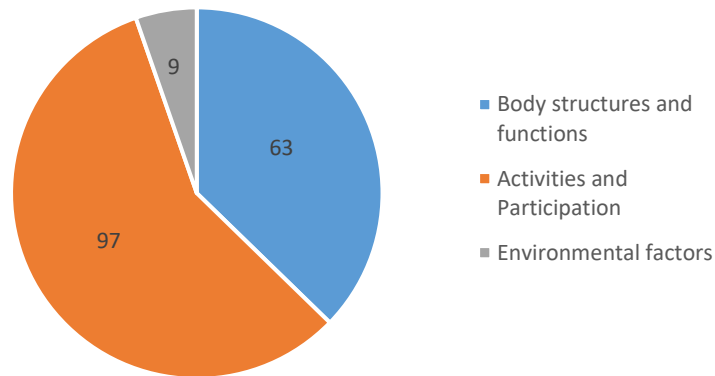


Figure 6-18 COPM Goals set at baseline showing the number of goals within each ICF Domain
Figure shows that within 169 goals set the majority (57.4%) were in the Activity and Participation domain

The individual goals identified by each child were given two baseline scores; COPM Performance (COPM-P) which evaluated the pre BoNT-A treatment evaluation of goal Performance and a COPM Satisfaction score (COPM-S) which evaluated how satisfied the CYPwCP and their families were with that goal performance at the time of the assessment.

COPM scores are highly personal and are dependent on the nature and complexity of the individual problems that children and families identify as an issue at the time of BoNT-A treatment. This ensures a highly individualised approach to goal setting, one child’s score cannot therefore be easily compared with another. The only clinically meaningful comparison is a child’s individual score change from baseline assessment to subsequent re-assessments.

COPM-P and COPM-S scores were evaluated at each post BoNT-A assessment time point and scored (1-10). Scores were also classified in terms of whether there had been any change in goal attainment at each assessment time point following injections in comparison to their baseline pre-injection COPM scores.

The MCID for the COPM is a change score of two or more points (Law et al., 2015), therefore in order to align responses for analysis, all COPM scores were rated in comparison to baseline pre-injection scores at each time point:

- Goal scores that decreased by at least two points were classified as “deteriorated”
- Goal scores that improved by at least two points were classified as “responder”
- Goal scores that did not reach MCID levels (≤ 2) were classified as “non responder”

6.2.1 COPM Scoring- An evaluation of averaged and total COPM goal scores

Average Goal attainment scores

The standard method of calculating both the Performance and Satisfaction COPM scores is by summing up a child’s individual goal scores and dividing by the total number of goals set to gain an averaged total score for COPM Performance and COPM Satisfaction at each time point (Law et al., 1995b).

Change scores for both COPM Performance and Satisfaction were calculated following BoNT-A injections at assessments T1-T3. Each child’s average goal attainment was subsequently classified into 3 categories as highlighted above; “responder”, “non-responder” or “deteriorated” for both COPM Performance and Satisfaction scores at each follow-up point dependent on the change from scores set at baseline (before BoNT-A treatment). All changes were interpreted relative to the MCID of ≥ 2 as recommended by the test developers (Law et al., 2005).

Goal attainment for children in the study using change in *average* goal scores is summarised in Table 6-11. This indicates the percentage of children whose change in average goal scores from baseline (relative to the MCID) was classified as responder/non-responder/deteriorated at each post injection time point (T1-T3).

Individual Goal Attainment scores

Whilst it is accepted practice to analyse average total COPM scores to evaluate change in both the paediatric and adult population (Kang et al., 2020), there is some concern, particularly in the heterogeneous cerebral palsy population, that averaged COPM scores may not provide the same degree of responsiveness as examining change at an individual goal level (Damiano, 2014) and important information about goal attainment may be lost.

This is particularly pertinent when evaluating outcome following an intervention such as BoNT-A. The types of goals identified may vary in complexity (e.g., climbing a kerb versus riding a bike without stabilizers). It may not therefore be very meaningful to add scores across a variety of problems, as responsiveness to individual goals can be lost. Improvement in one goal may be averaged out by no response or deterioration in another goal. Attainment in one goal may be cancelled out by deterioration in another goal. Looking for change between assessments for each goal may provide more relevant information.

Changes in COPM Performance and Satisfaction scores for each of the 169 individual goal scores from T0 to T1-T3 were also evaluated. These individual goals were also categorised and classified as “deteriorating”, “not responding” or “responding” following BoNT-A relative to the MCID ≥ 2 point change and have been summarised in Table 6-12.

Analysis of individual goals permitted the change to be evaluated relative to each individual goal set in an attempt to preserve detail of individual goal change post intervention at each time point.

Table 6-11 Response to BoNT-A for averaged COPM Performance and Satisfaction scores

	PERFORMANCE % (n= number of children*)			SATISFACTION % (n= number of children*)		
	T1	T2	T3	T1	T2	T3
Total sample n=64						
Responder	59.4 (38)	45.3 (29)	54.7 (35)	62.5 (40)	45.3 (29)	56.3 (36)
Non-responder	34.4 (22)	45.3 (29)	31.3 (20)	31.3 (20)	45.3 (29)	31.3 (20)
Deteriorated	0 (0)	1.6 (1)	3.1 (2)	0 (0)	1.6 (1)	1.6 (1)
Missing data	6.2 (4)	7.8 (5)	10.9 (7)	6.2(4)	7.8 (5)	10.9 (7)
Total scored	93.8 (60)	92.2 (59)	89.1 (57)	93.8 (60)	92.2 (59)	89.1 (57)

*number of families scoring COPM at clinical assessment

NB ** one child had a fractured ankle and family could not score COPM@T2

Table 6-12 Response to BoNT-A for individual COPM Performance and Satisfaction scores

	PERFORMANCE % (n= number of individual goals)			SATISFACTION % (n= number of individual goals)		
	T1	T2	T3	T1	T2	T3
Total number of goals n=169						
Responder	65.7 (111)	52.7 (89)	58.6 (99)	62.1 (105)	51.5 (87)	59.8 (101)
Non-responder	27.2 (46)	35.5 (60)	25.4 (43)	30.8 (52)	33.7 (57)	24.8 (42)
Deteriorated	1.2 (2)	3.6 (6)	3.6 (6)	1.2 (2)	6.5 (11)	3.0 (5)
Missing data	5.9 (10)	8.3 (14)	12.4 (21)	5.9 (10)	8.3 (14)	12.4 (21)
Total scored	93.5 (158)	91.7 (155)	87.6 (148)	93.5 (158)	91.7 (155)	87.6 (148)

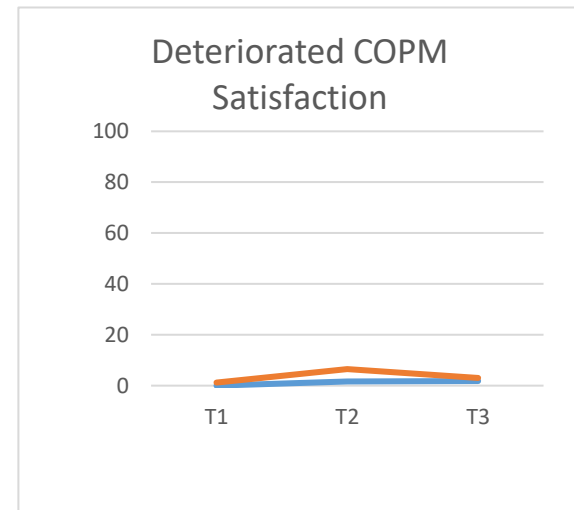
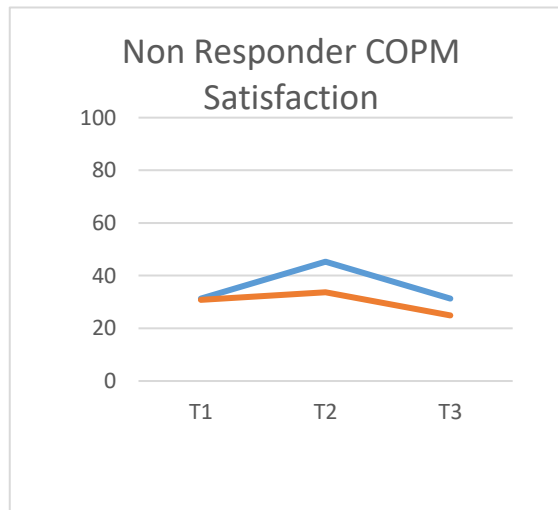
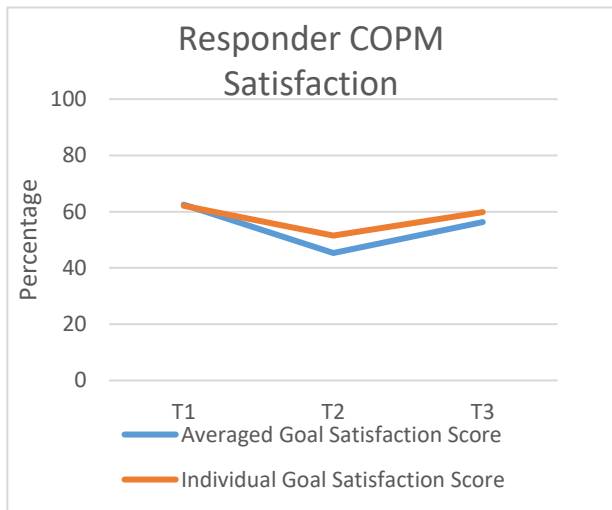
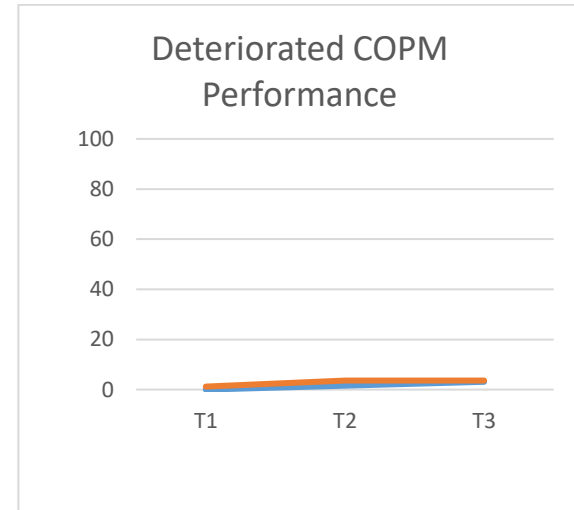
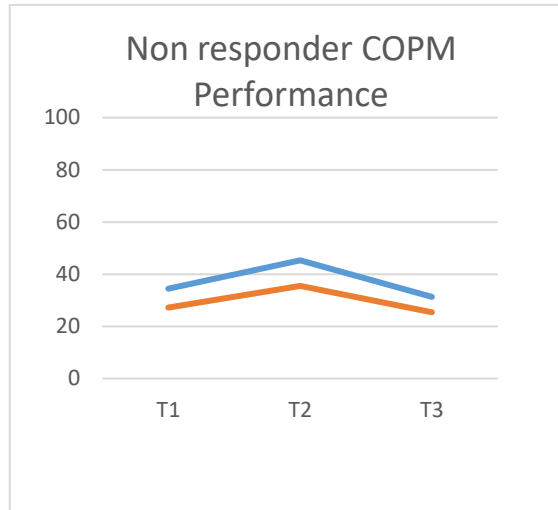
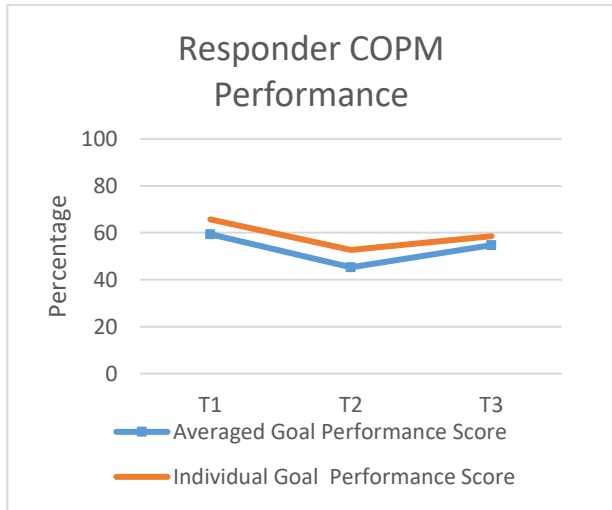


Figure 6-19 COPM Response Total Individual Goal (orange) vs Average Goal Score (blue)

The percentages of responding, non-responding and deteriorating goals were mapped for both COPM Performance and COPM Satisfaction scores using both averaged and individual goal score methods in comparison to baseline scores. The findings of applying these two methods for assessing goal attainment are shown in Figure 6-19.

Although similar trends of response were seen, goal attainment as measured by change in individual goal scores appeared to show a higher percentage of goals that had been classified as responders for both COPM-P and COPM-S and a lower percentage of goals classified as non-responders in comparison to assessing goal attainment via average goal scores. The data suggested that using averaged goal scores methods could result in an overestimation of non-responders as fine detail regarding individual scores may be lost.

Within the research literature a change in average COPM score following intervention is usually reported. However, in the clinical setting there is an advantage in using individual goal scores, as this allows goals to be categorised into ICF domains, detail that is lost with averaged goal scores. This permits further investigation of change post BoNT-A injection within the different domains of the ICF which can provide more meaningful information when evaluating the effects of BoNT-A and supporting individualised patient care targeting goals which are important to children and families (Damiano, 2014).

In order to compare results with published work in the field, most of the statistical analysis within the study (including multilevel regression analysis in Chapter 8 (8.1.2)) has used the traditional method of using average scores to investigate change in COPM Performance and Satisfaction. However, a further analysis using individual COPM scores has also been reported later in this chapter in order to investigate any differences in response between the ICF domains.

6.2.2 Comparison of averaged COPM Performance and Satisfaction scores between baseline and post BoNT-A intervention over twelve months

A one-way repeated measures ANOVA was conducted to evaluate change in COPM Performance and Satisfaction scores over the twelve months. The main effect of time was significant for both COPM-P and COPM-S, showing a statistically significant difference in scores across the four time points (T0-T3). The results are summarised in Table 6-13 and suggest a large effect size as shown by the Partial Eta Squared values (η_p^2) across both COPM scores (Cohen, 2013)

As the assumption of sphericity by Mauchly’s test was not met in the case of COPM-P or COPM-S, a repeated measures ANOVA with a Greenhouse-Geisser correction was applied.

n=49	F	p-value	Partial Eta Squared η_p^2	Mauchly’s test of Sphericity
COPM-P*	F (2.49,119.36) = 46.06	<0.001	0.49	0.002
COPM-S*	F (2.60,124.92) = 36.73	<0.001	0.43	0.042
* Greenhouse-Geisser correction				

Table 6-13 One way repeated measures ANOVA for Averaged COPM scores (effect of Time)

Boxplots showing a change in COPM-P and COPM-S scores over 12 months are shown in Figure 6-20. These demonstrated an improvement in scores from baseline at all three post injection time points T1 -T3, with an outlier observed at baseline COPM-S only.

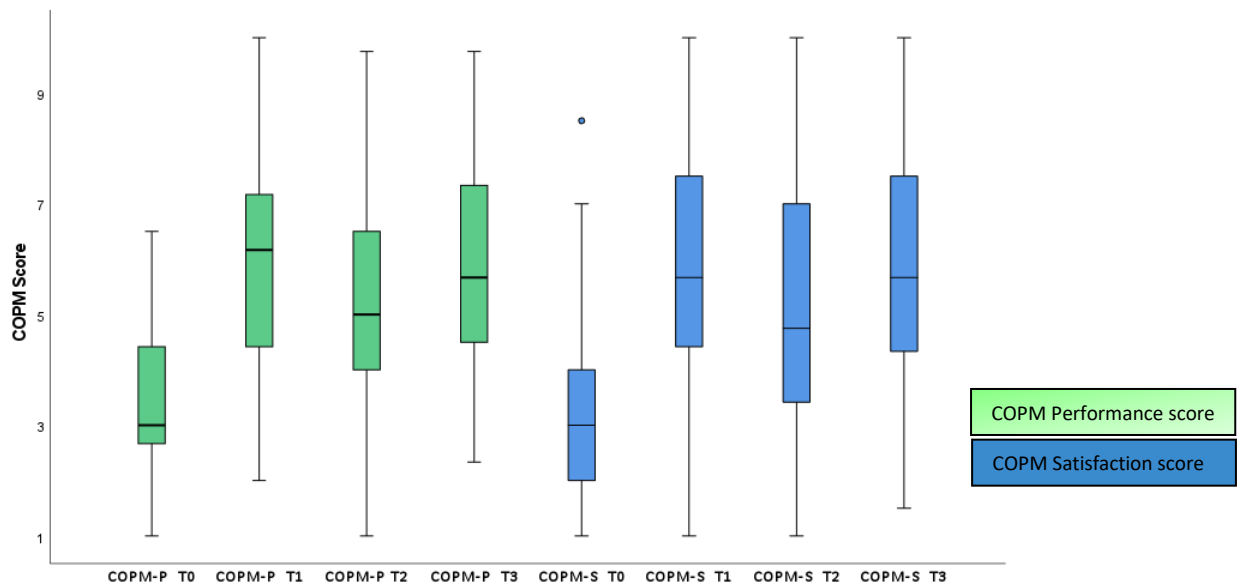


Figure 6-20 Boxplot showing improvement from baseline (T0) in COPM P (performance) scores and COPM S (satisfaction scores). Significant improvement was seen in COPM P and S at T1-T3 ($p < .001$)*an outlier observed at baseline COPM-S

COPM -Performance Scores

There was a statistically significant improvement in COPM Performance scores from baseline T0 (pre- injection) (mean=3.4, SD 1.40) to T1, six weeks (mean=6.04, SD 1.9), T2 six months (mean=5.3, SD 1.82) and T3 twelve months post injection (mean=5.98 SD 2.01) (Figure 6-21).

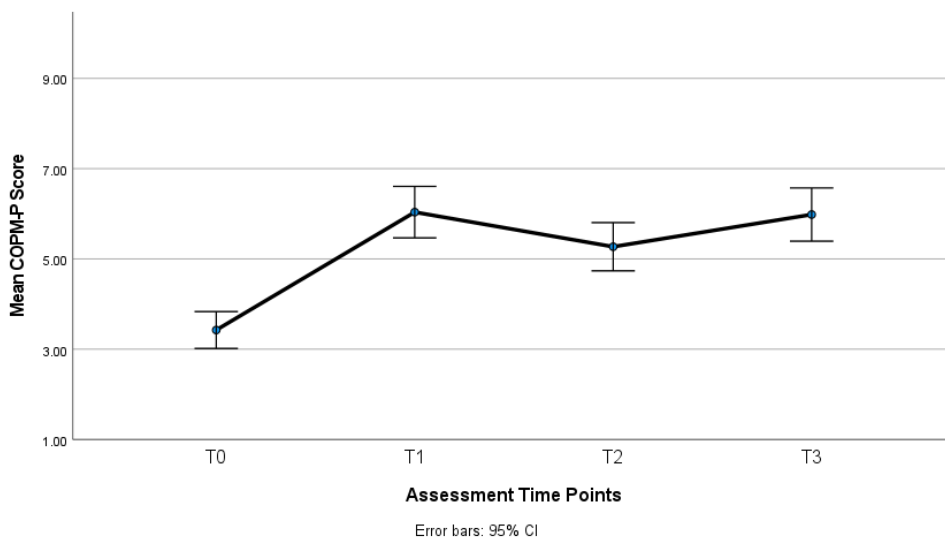


Figure 6-21 Mean COPM Averaged Performance Scores. Repeated measures ANOVA demonstrated significant improvement from baseline. Post hoc analysis with a Bonferroni adjustment showed COPM Performance scores were statistically significantly increased at all post injection time points ($p < .001$)

Post hoc analysis with a Bonferroni adjustment revealed that COPM Performance scores were statistically significantly increased at all post injection time points ($p<.001$). Whilst all time points were statistically significant, only the changes in COPM Performance at six weeks (T1) and twelve months (T3) post injection exceeded the MCID change score of 2 points, suggesting that the improvement six months post injection may not have been clinically significant (Table 6-14).

Assessment Time Point	COPM P change score	95% Confidence Interval	Statistical significance	Clinical significance
T1	2.6	[2.0,3.3]	<.001	>2
T2	1.9	[1.3,2.5]	<.001	-
T3	2.6	[1.7,3.4]	<.001	>2

Table 6-14 Mean change Averaged COPM Performance Score

COPM -Satisfaction Scores

There was also a statistically significant improvement in COPM Satisfaction scores from baseline (pre- injection) (mean=3.2, SD 1.51) to T1, six weeks (mean=5.94, SD 2.20), T2 six months (mean=5.2, SD 2.29) and T3 twelve months post injection (mean=5.98 SD=2.27)

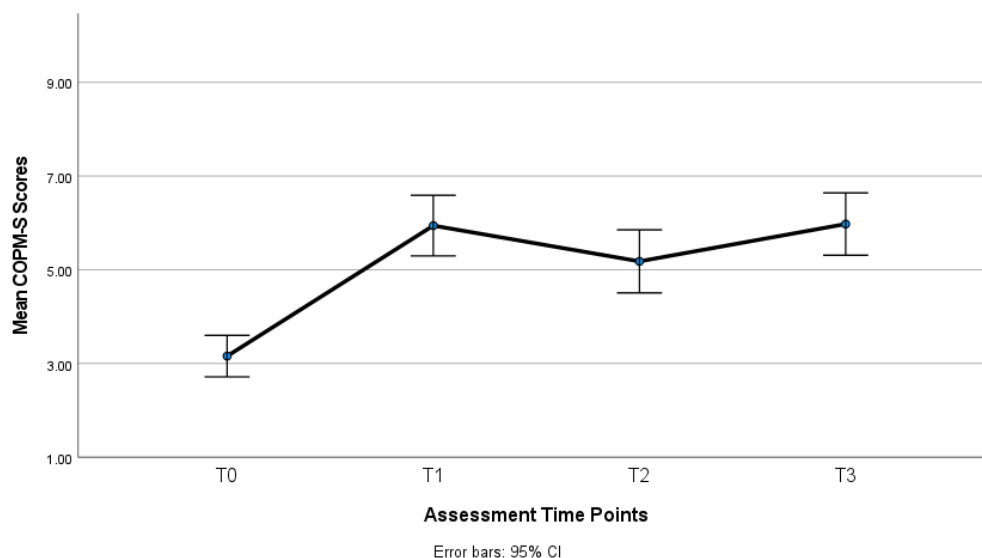


Figure 6-22 Mean COPM Averaged Satisfaction Score.

Post hoc analysis with a Bonferroni adjustment showed COPM Satisfaction scores were statistically significantly increased at all post injection time points ($p<.001$)

Post hoc analysis with a Bonferroni adjustment revealed that COPM Satisfaction scores were statistically significantly increased at all post injection time points (Table 6-15).

Assessment Time Point	COPM S change score	95% Confidence Interval	Statistical significance	Clinical significance
T1	2.8	[1.9,3.7]	<.001	>2
T2	2.1	[1.2,2.9]	<.001	>2
T3	2.8	[2.0,3.7]	<.001	>2

Table 6-15 Mean change Averaged COPM Satisfaction scores

Unlike COPM-P scores, COPM-S changes at all post injection time points (T1-T3) exceeded the MCID score of 2 points suggesting meaningful clinical change following BoNT-A injections at 6 weeks which were maintained at 6 and 12 months

Single cycle versus re-injection within the study

All children with a complete data set for COPM were included for statistical analysis (n=49). However, from a clinical perspective it was interesting to determine whether there was any significant difference in COPM scores for those children who received re-injection within the study and those children who only required a single injection cycle. Further subgroup analysis was performed between the two groups and is presented in Figure 6-23 for average COPM-P scores and in Figure 6-24 for averaged COPM-S.

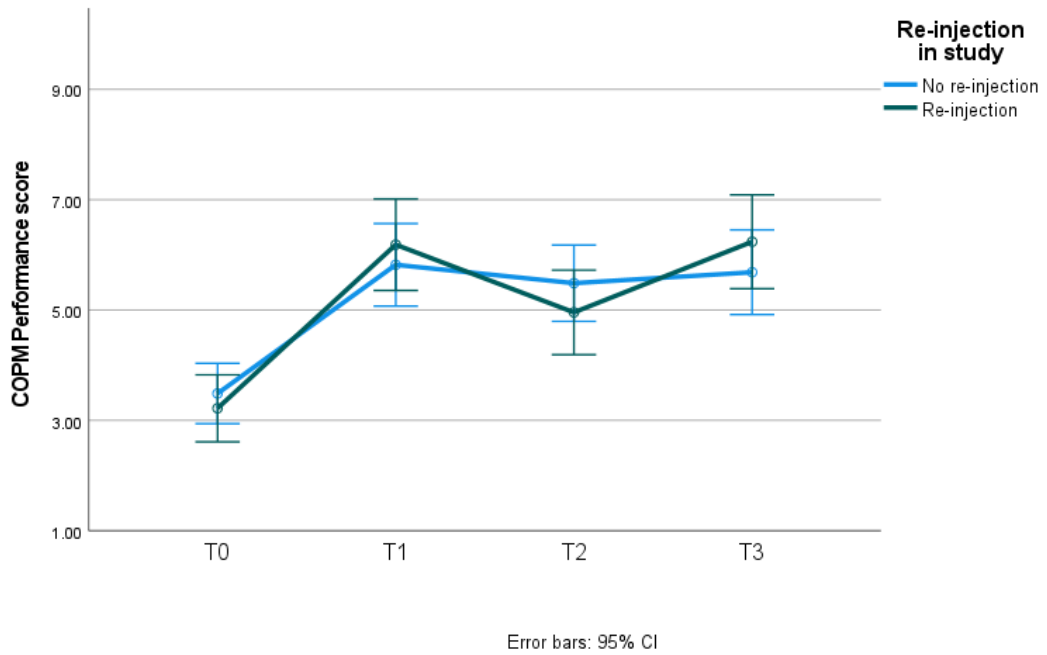


Figure 6-23 Mean Averaged COPM Performance score by re-injection within the study.
 The scores were not significantly difference between the two groups (re-injected and single injection in the study) at any time point ($p=.92$)

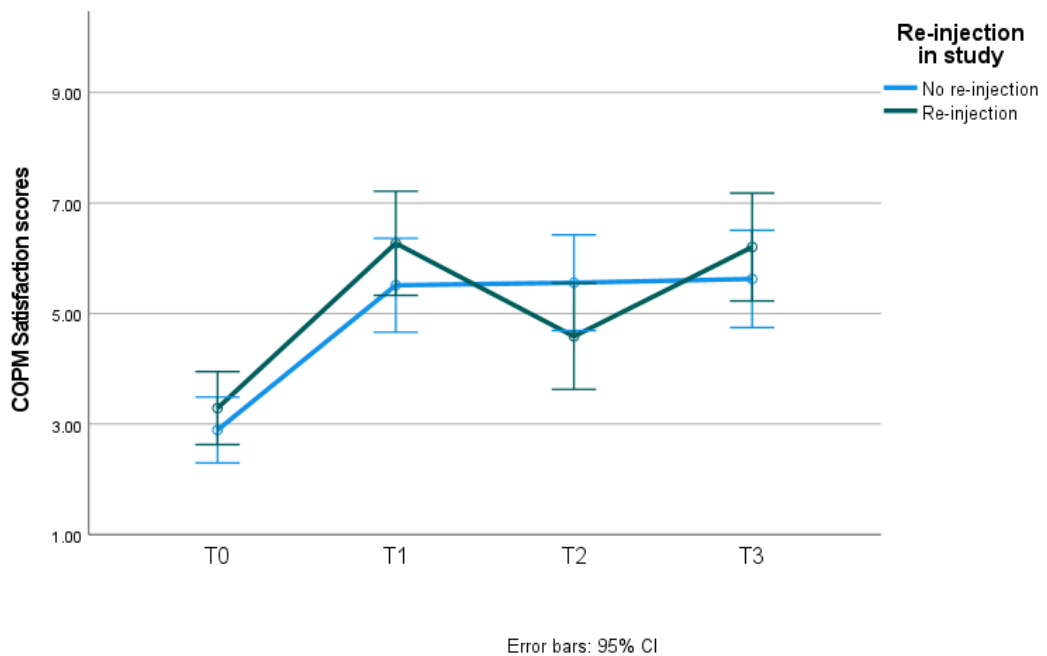


Figure 6-24 Mean Averaged COPM Satisfaction score by re-injection within the study
 The scores were not significantly difference between the two groups (re-injected and single injection in the study) at any time point ($p=.52$)

Interestingly, children who had re-injection within the study scored higher on average initially post injection at T1 but had a more marked reduction in both COPM Performance and Satisfaction scores at the T2 assessment in comparison to those children who only had a single injection cycle. Although this difference between the two groups was not statistically significantly different at any time point, children who had re-injection did not achieve MCID at T2 in either COPM Performance or Satisfaction scores, whereas those who did not require re-injection did. This would suggest that one of the drivers for re-injection may be linked to goal attainment and satisfaction scores as rated by CYPwCP and their families.

GMFCS level

COPM scores showed improvement at all time points for children in GMFCS Levels I-III for both COPM Performance (Figure 6-25) and Satisfaction scores (Figure 6-26) but these scores in contrast to the QFM attribute scores were not significantly different between the GMFCS levels.

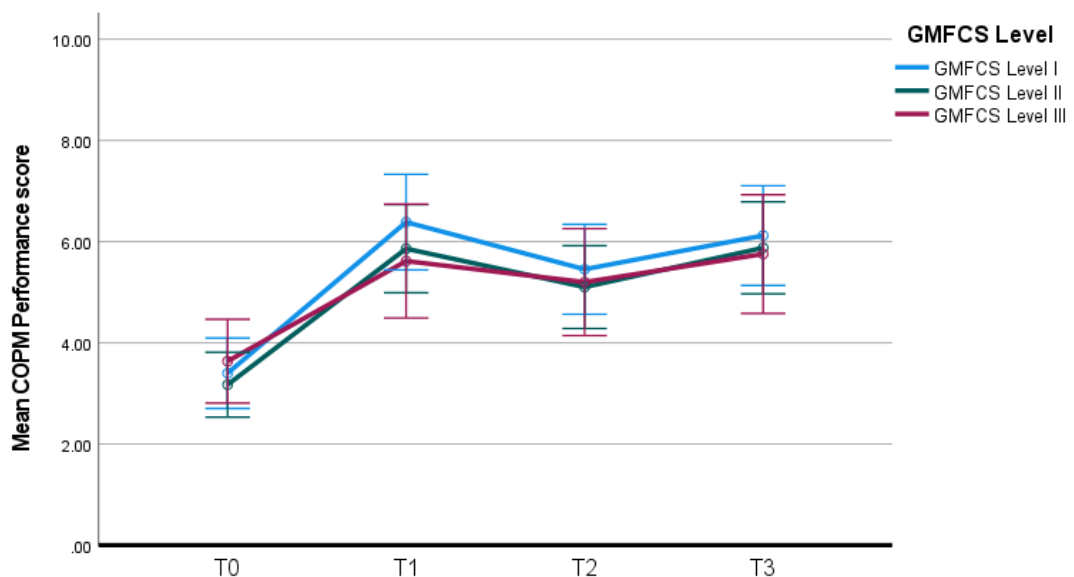


Figure 6-25 COPM Performance scores over 12 months by GMFCS Level. The difference between GMFCS levels was not statistically significant ($p=.73$)

However, the change in COPM -P scores for GMFCS Level I children exceeded MCID values at all-time points post injection, suggesting clinical significance across the twelve months. In contrast, children in GMFCS Levels II and III only showed clinically significant improvement from baseline scores at T1 and T3.

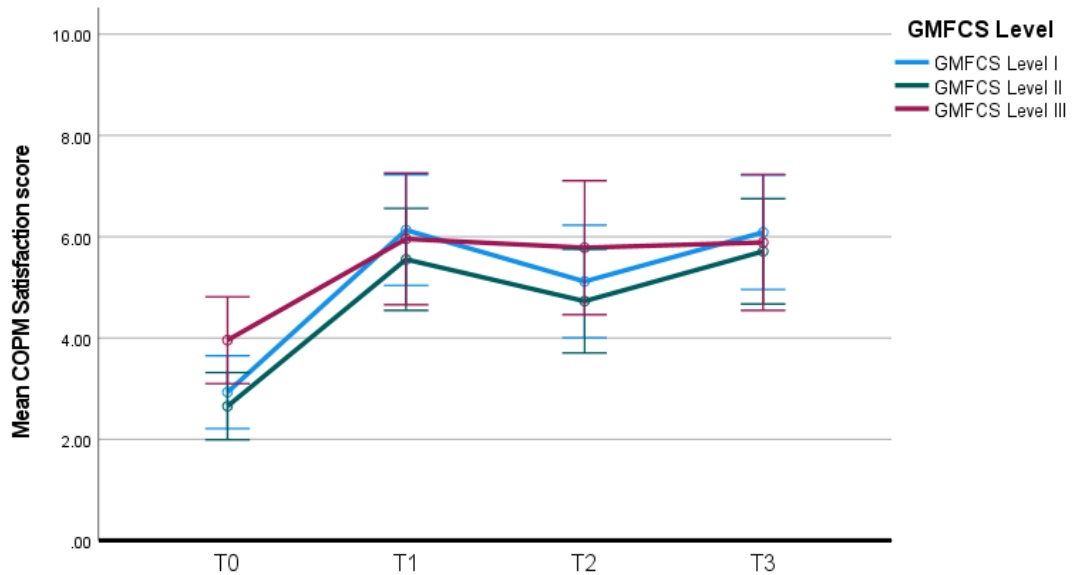


Figure 6-26 COPM Satisfaction scores over 12 months by GMFCS Level.
The difference between GMFCS levels was not statistically significant ($p=.53$)

For GMFCS Level I and II children change in COPM -S scores exceeded MCID values at all time points post injection suggesting a clinically significant improvement in satisfaction with goal performance across twelve months. While children in GMFCS Level III only showed clinically significant improvement at T1 from baseline scores. This suggests that improvement in performance for children in GMFCS Level III exceeded MCID at 6 weeks and although this appeared to be maintained was only associated with a significant change in parental satisfaction at 6 weeks post BoNT-A.

6.2.3 COPM Analyses using Individual Goal scores

The data were also analysed using the 169 individual goal scores which provided the opportunity to examine response within the different ICF domains.

As can be seen in Figure 6-27 the distribution of goal type appeared similar between the GMFCS levels. A Kruskal-Wallis Test was conducted and determined there was no significant difference in goal type chosen between the GMFCS levels ($p=.60$).

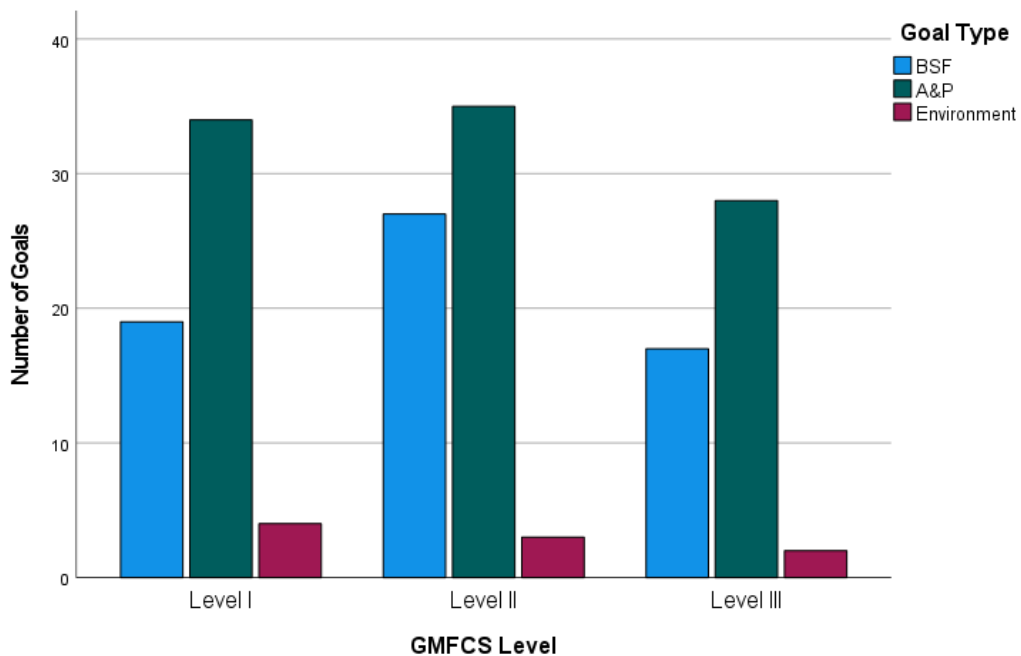


Figure 6-27 COPM Goal type by ICF Domain and GMFCS Level.
There was no significant difference between the GMFCS levels in ICF goal type chosen ($p=.60$)

A one-way repeated measures ANOVA was conducted to evaluate change in individual COPM Performance and Satisfaction scores over the twelve months. The main effect of time was once again significant for both COPM-P and COPM-S, showing a statistically significant difference in scores across the four time points (T0-T3).

The results are summarised in Table 6-16 and suggest a large effect size as shown by the Partial Eta Squared values (η_p^2) across both COPM scores (Cohen, 2013). As the assumption of sphericity by Mauchly's test was not met in the case of COPM-P a repeated measures ANOVA with a Greenhouse-Geisser correction was applied.

n=129	F	p-value	Partial Eta Squared η_p^2	Mauchly's test of Sphericity
COPM-P*	F (2.72,384.42)=81.11	<0.001	0.39	0.001
COPM-S	F (3, 384) = 66.97	<0.001	0.34	0.181
* Greenhouse-Geisser correction				

Table 6-16 One way repeated measures ANOVA for Individual COPM scores (effect of Time)

Individual COPM -Performance Scores

There was a statistically significant improvement in COPM Performance scores from baseline T0 (mean=3.29 SD 1.76) to 6 weeks post BoNT-A (mean=5.93 SD 2.32). Improvement from baseline was maintained at 6 months (mean=5.29 SD 2.16) and 12 months (mean=6 SD 2.35) (Figure 6-28).

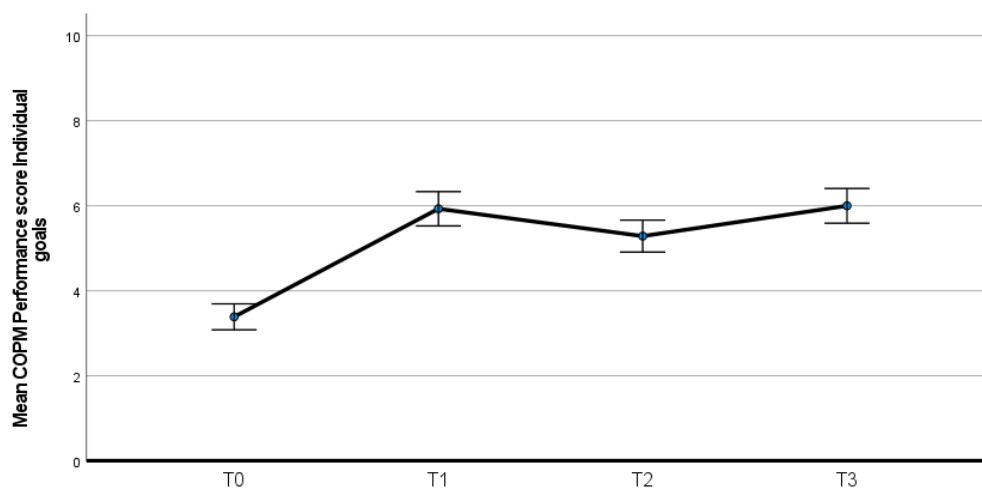


Figure 6-28 COPM Performance scores for Individual goals.

A significant improvement in COPM Performance score was observed from baseline at all time points ($p < .001$)

Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons. As with averaged COPM-P scores, these were statistically significantly improved at all assessment time points following BoNT-A injections $p < 0.001$ (Table 6-17). These change scores also reached clinical significance at 6 months whereas averaged scores did not. This could suggest an increased sensitivity when analysing individual goal changes in comparison to averaged goal scores.

Assessment Time Point	COPM P change score	95% Confidence Interval	Statistical significance	Clinical significance
T1	2.5	[2.1,3.0]	<.001	>2
T2	2.0	[1.4,2.4]	<.001	>2
T3	2.6	[2.0,3.2]	<.001	>2

Table 6-17 Mean change Individual COPM Performance Score

Individual COPM -Satisfaction Scores

COPM satisfaction scores followed a similar trend with statistically significant increases between baseline pre BoNT-A at T0 (mean =3.09 SD 1.86) and all post injection assessments T1 (mean =5.78 SD2.58), T2 (mean = 5.16 SD 2.67) and T3 (mean =5.99 SD 2.61).

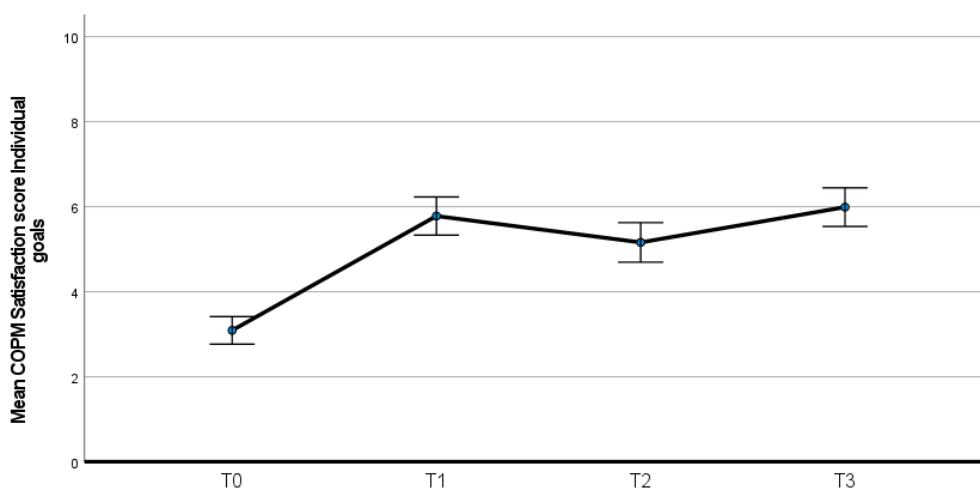


Figure 6-29 COPM Satisfaction scores for Individual Goals.

A significant improvement in COPM Satisfaction score was observed from baseline at all time points ($p < .001$)

Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons. As with averaged COPM-S scores, improvement in individual scores were found to be clinically significant at all time points from baseline (Table 6-18).

Assessment Time Point	COPM S change score	95% Confidence Interval	Statistical significance	Clinical significance
T1	2.7	[2.1,3.3]	<.001	>2
T2	2.1	[1.4,2.7]	<.001	>2
T3	2.9	[2.3,3.5]	<.001	>2

Table 6-18 Mean change Individual COPM Satisfaction scores

ICF Domains

As illustrated above, COPM Performance and Satisfaction scores generally followed a similar pattern independent of the method used (Averaged score or Individual Goals score). However, further subgroup analysis of ICF domains showed a difference in the timing of response between the ICF domains (Figure 6-30 & 6-31)

Whilst all goals significantly improved from baseline across 12 months ($p < .001$), COPM goal scores within BSF and Environment domains appeared to show more fluctuation than those in Activity and Participation (A&P) domains. COPM-P goal scores showed greater improvement in BSF and Environment domains at T1 (6 weeks post injection), which could be associated with a reduction in spasticity following BoNT-A but these scores then dropped between T1 and T2 at six months, whereas A&P goal scores, once improved at six weeks, were maintained throughout the 12 months. A similar trend was shown in COPM-S scores.

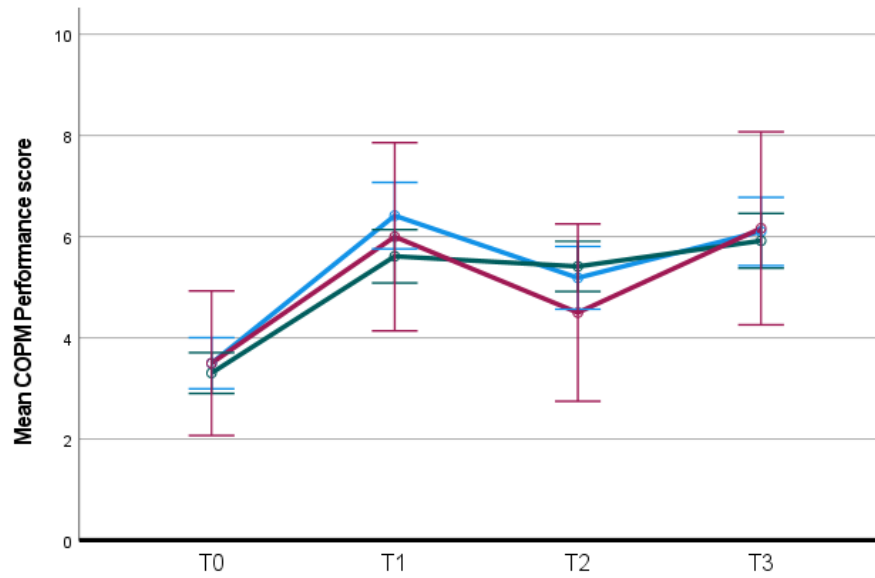


Figure 6-30 Individual COPM Performance scores by ICF Domain (n=129)
 All goals significantly improved from baseline across 12 months ($p < .001$)

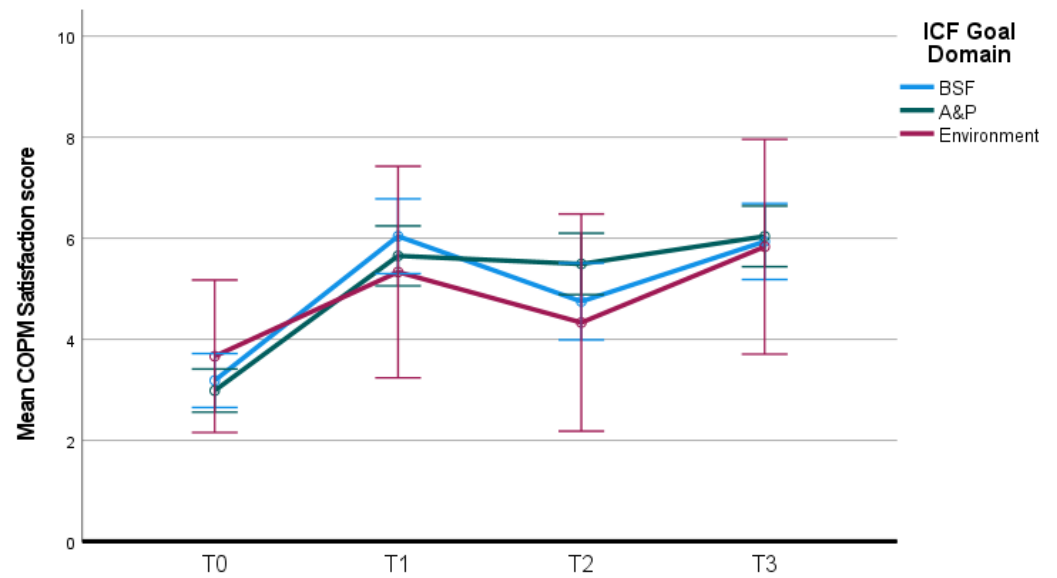


Figure 6-31 Individual COPM Satisfaction scores by ICF Domain (n=129)
 All goals significantly improved from baseline across 12 months ($p < .001$)

As can be seen in Table 6-19 clinically significant improvement was seen in all COPM-P scores in all domains at T1 (six weeks) however, only A&P goals showed clinically significant improvement at six months (T2).

COPM-P	Baseline T0	6 weeks T1	6 months T2	12 months T3
Mean (SD)				
BSF n=63	3.59 (1.74)	6.42 (2.05)*	5.14 (2.11)	6.09 (2.02)*
A&P n=97	3.35 (1.69)	5.71 (2.40)*	5.42 (2.11)*	5.87 (2.41)*
Environment n=9	3.38 (1.87)	5.63 (3.72)*	4.33 (4.08)	5.38 (2.93)*
* change score \geq MCID				

Table 6-19 Mean Individual COPM Performance Scores by ICF Domain

COPM-P scores improved again at T3, 12 months post injection and once again suggested a clinically significant improvement in all ICF domains. It is of note that there was an increase in scores for children who had a single injection as well as those who had re-injection, with no statistically significant difference between the two groups. However as can be seen in Figure 6-32 the greatest improvement was seen in the BSF goals for re-injected children. However, this was less marked for A&P goals (Figure 6-33).

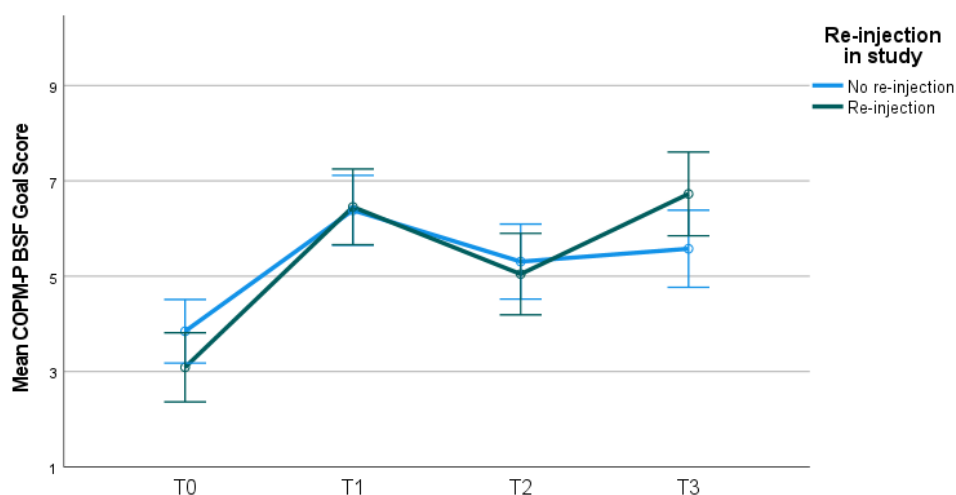


Figure 6-32 Mean COPM-P BSF Goal Score by re-injection within the study.

There was no statistically significant difference observed between the two groups ($p=.48$)

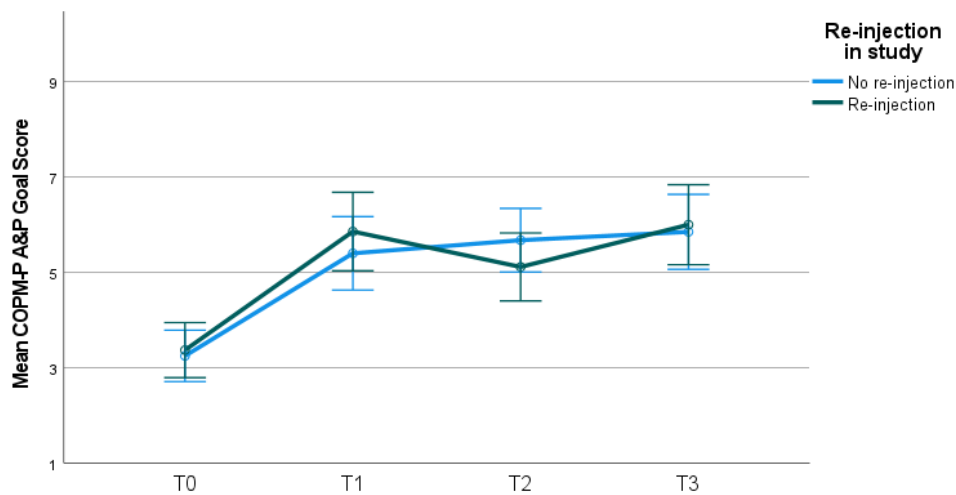


Figure 6-33 Mean COPM-P A&P Goal Score by re-injection within the study. There was no statistically significant difference observed between the two groups (p=.43)

COPM Satisfaction (COPM-S) scores followed a similar trend (Table 6-20). Once again only goals related to activity and participation showed clinically significant improvement from baseline at all time points. BSF and Environment COPM-S change scores did not reach clinical significance at T2. However, there were few Environment goals (which were all related to improved splint tolerance) with a large variability in response, which could affect the interpretation of these results.

COPM-S	Baseline T0	6 weeks T1	6 months T2	12 months T3
Mean (SD)				
BSF n=63	3.10 (1.80)	6.09 (2.30)*	4.8 (2.64)	5.89 (2.35)*
A&P n=97	3.06 (1.69)	5.73 (2.64)*	5.53(2.71)*	5.98 (2.70)*
Environment n=9	3.67 (1.86)	5.38 (3.25)*	4.33 (4.08)	5.83 (2.93)*

Table 6-20 Mean Individual COPM Performance Scores by ICF Domain
* scores \geq MCID suggesting minimal clinically important difference had been reached

Similar trends for re-injection were also seen for COPM-S scores for BSF goals (Figure 6-34)

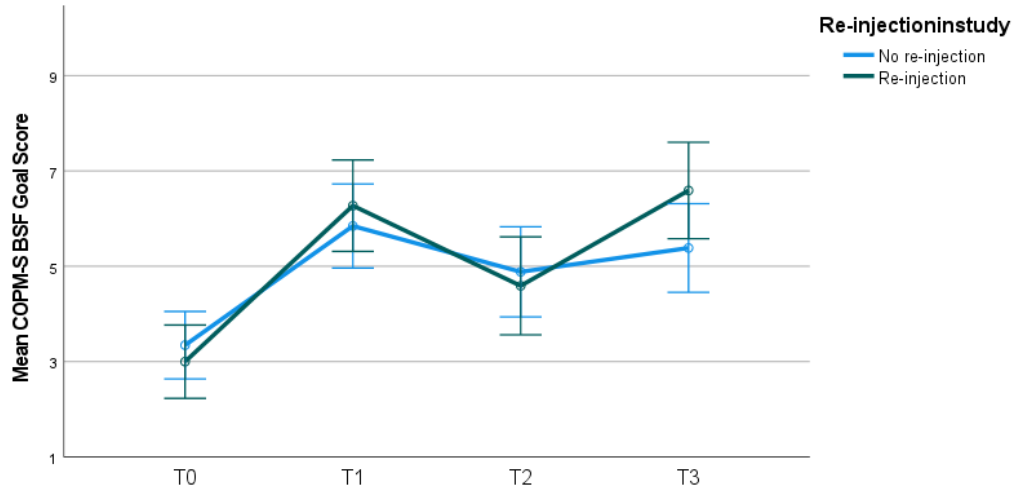


Figure 6-34 Mean COPM-Satisfaction BSF Goal Score by re-injection within the study
There was no statistically significant difference between the two groups ($p=.82$)

and within A&P goals (Figure 6-35)

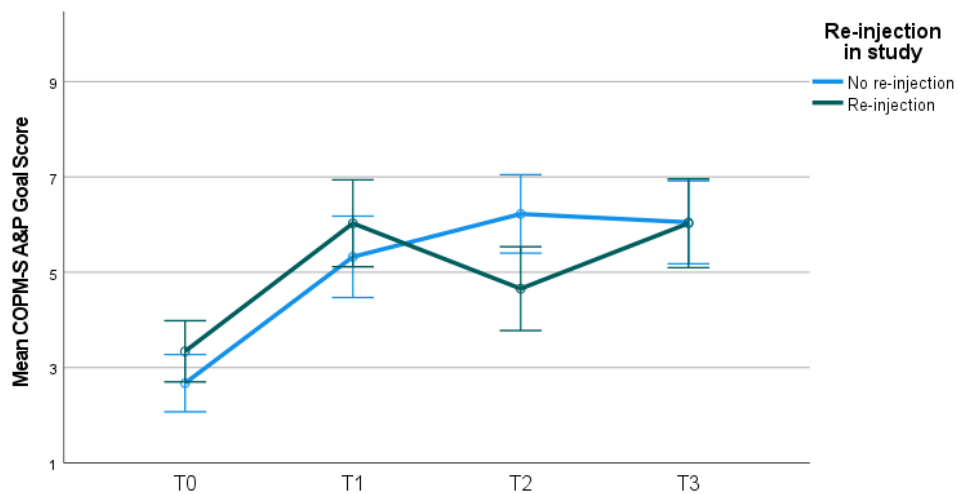


Figure 6-35 Mean COPM-S A&P Goal Score by re-injection within the study
There was no statistically significant difference between the two groups ($p=.09$)

It appears that deterioration in BSF goals addressing spasticity and associated decline in A&P goals could contribute to decision making with respect to re-injection at six months post injection.

COPM Performance scores and clinical response

When evaluating change using MCIDs it can also be clinically useful to identify the percentage of goals that have been classified as responder, non-responder and deteriorated (relative to MCID status), in order to inform clinical practice (McLeod et al., 2011). The results for this study are categorised within the ICF-CY domains across the twelve months following BoNT-A treatment (Figure 6-36). COPM Performance scores remained most stable across both activity and participation goals. The percentage of goals classified as responders at 6 weeks post injection (67%) remained constant at 6 months (64%) and 12 months (64.7%), suggesting that once a child’s activity and participation goals were achieved, they were maintained throughout the 12 months. Other ICF domains showed greater variability with a reduction in the percentage of body structure and function (BSF) and environmental goals classified as responders at 6 months. This may suggest that re-injection occurs as a result of evaluation of BSF changes rather than activity and participation changes at 6 months.

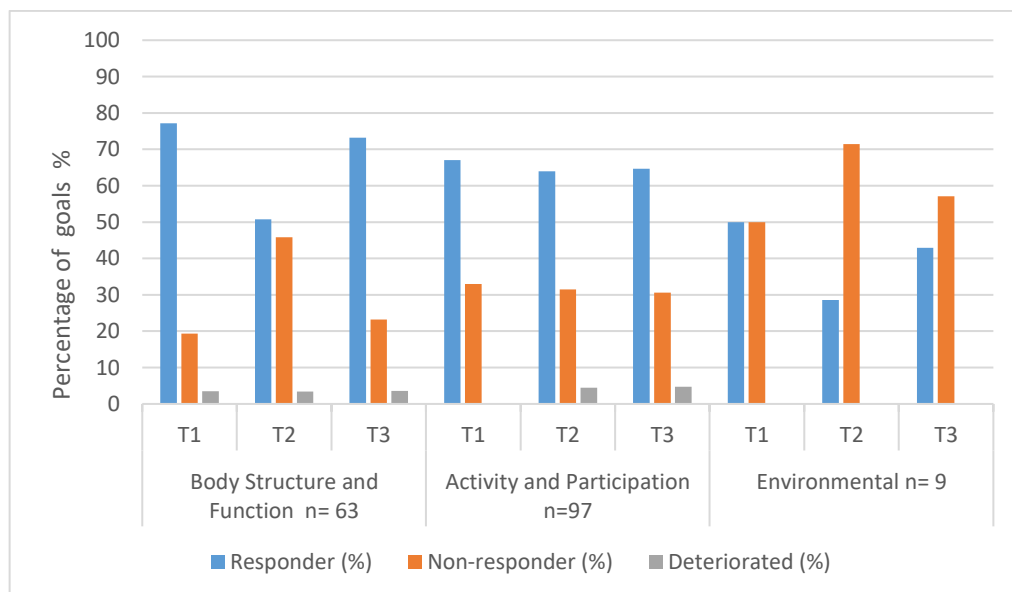


Figure 6-36 COPM Performance Scores response status by ICF Goals over 12 months post BoNT-A

Summary

QFM

- QFM change scores demonstrated statistically significant improvement in all attribute scores following BoNT A injections at 6 weeks which were maintained at 6 months and 12 months
- QFM changes were clinically significant for Alignment, Co-ordination and Weight-shift at all post injection time points 6 weeks, 6 months and 12 months post injection
- QFM changes in Stability, Dissociated Movement only showed clinically significant improvement at 6 months which was maintained at 12 months
- Children within all GMFCS levels I-III demonstrated significant improvement in QFM attribute scores over 12 months following BoNT-A treatment.
- QFM was able to discriminate between GMFCS Levels. QFM attribute scores were significantly higher in children in both GMFCS levels I and II than those in GMFCS Level III. However only the QFM attribute scores of Co-ordination and Dissociated movement could discriminate between GMFCS levels I and II.

COPM

- COPM goal performance and satisfaction scores demonstrated statistically significant improvement from baseline over 12 months following BoNT-A injections
- Change in averaged COPM Performance scores suggested clinically significant improvement at 6 weeks and 12 months post injection but change scores from baseline were not clinically significant at 6 months
- Change in averaged COPM Satisfaction scores suggested clinically significant improvement at 6 weeks post injection and remained clinically significant at 6 and 12 months
- Individual COPM goal scores relating to Activity and Participation domains of the ICF showed statistical and clinically significant improvement following

BoNT-A injections at 6 weeks and these were maintained at 6 and 12 months suggesting long term improvement in Activity and Participation goals

- Individual COPM goal scores relating to Body structure and Function domain of the ICF demonstrated clinically significant improvement following BoNT-A injections at 6 weeks, but this was no longer clinically significant at 6 months suggesting a shorter-term improvement in Body structure and Function goals than goals in the Activity and Participation domains.

Chapter 7 Results Phase I: Secondary Outcome Measures

7.1 Results

Data from secondary outcome measures reflecting all ICF domains (Body function and structure, Activity and Participation) were collected and these are detailed in Chapter 4 (4.2.2). These outcome results are summarised within the individual ICF domains (Table 4-2). Continuous data were analysed using a one-way repeated measures ANOVA and ordinal data using the Friedman test, with Bonferroni corrections for multiple comparisons.

7.2 Body function and structure (BSF)

Individual BSF outcomes used in the study are considered individually within this section.

- **Spasticity:** Modified Tardieu scale (MTS), Modified Ashworth Scale (MAS)
- **Muscle selectivity:** Selective Motor Control (SMC)
- **Pain:** Faces Pain Scale - Revised (FPS-R), CPQOL Pain domain

As this was a pragmatic clinical study, there were a number of different muscle groups injected (Table 5-5). This heterogeneity of BoNT-A treatment within the study presented a challenge for analysis of change in spasticity following BoNT-A. There were a number of challenges as each muscle group had different standardised error of measurement values (SEM) making comparison of change difficult and some muscles were injected infrequently, preventing meaningful statistical analysis. The data was therefore analysed based on the most frequently injected muscles: gastrocnemius and hamstring muscles.

In order to capture the complexity of clinical practice the data was analysed in two different ways. Spasticity outcomes were first analysed evaluating change in the hamstring and gastrocnemius muscles injected (7.2.1) and this was then followed by a 'responder' analysis evaluating technical response following BoNT-A (7.3).

Descriptive statistics for all the Body structure and Function outcome (BSF) measures used within the study are based on the available data collected at each time point and are summarised in Table 7-1.

BSF outcome measures n= sample size per time point	ICF BSF	Baseline T0	T1 6 weeks	T2 6 months	T3 12 months	P main effect of time
Gastrocnemius MTS R1 Degrees Mean (SD)	Tone	-17.3 (7.8) (n=73)	-11.4 (11.1) *** (n=70)	-15.96 (10.7) (n=68)	-13.8 (8.5) (n=67)	<0.001
Gastrocnemius MAS Median (IQR)	Tone	3(3,4)	2 (1.75,3)***	3 (2,4)	3 (2,3)	<0.001
MTS R1 Hamstrings (degrees) Mean (SD)	Tone	83.6 (16.3) n=43	64.5 (13.8)*** n=43	72.2 (16.0)** n=41	71.5 (17.5)** n=39	<0.001
MAS Hamstrings Median (IQR)	Tone	3 (3,3)	2 (1,2)***	2 (1,3)***	2 (1,3)***	<0.001
SMC Median (IQR)	Muscle selectivity	2 (1,3) n=90	3 (2,3) n=85	3 (2,4)*** n=85	3 (2,4)*** n=78	<.001
Pain (m FPS) Mean (SD)	Pain	2.2 (2.4) n=64	1.2 (1.7)*** n=58	1.6 (2.4)* n=56	1.7 (2.4) n=54	=.001 [¥]
CPQOL Pain and disability % Mean (SD)	Pain	41.18 (15.46) n=64	34.24 (14.45)*** n=60	35.12 (17.56)** n=60	36.06 (15.79) n=57	=.001

***p<0.001 ** p<.0.01 *p<.05 Bonferroni test for multiple comparisons ¥ Greenhouse-Geisser correction

Table 7-1 Summary of descriptive statistics for Body Structure and Function (BSF) measures

7.2.1 Measures of Spasticity and hypertonicity

The aim of BoNT-A treatment is to reduce dynamic tone in a hypertonic (spastic) muscle. The clinical outcome measure used to detect a change in spasticity in the study was the R1 component of the MTS (Boyd and Graham, 1999) (Chapter 4, 4.2.2). The R1 value (measured in degrees) is also referred to as the ‘dynamic catch’, and is a proxy measure widely used in clinical practice to evaluate spasticity in the injected muscle (see 4.2.2). A reduction in the MTS R1 score represents a clinical improvement in the ‘dynamic catch’ of the injected muscle indicating less spasticity (Figure 7-1).

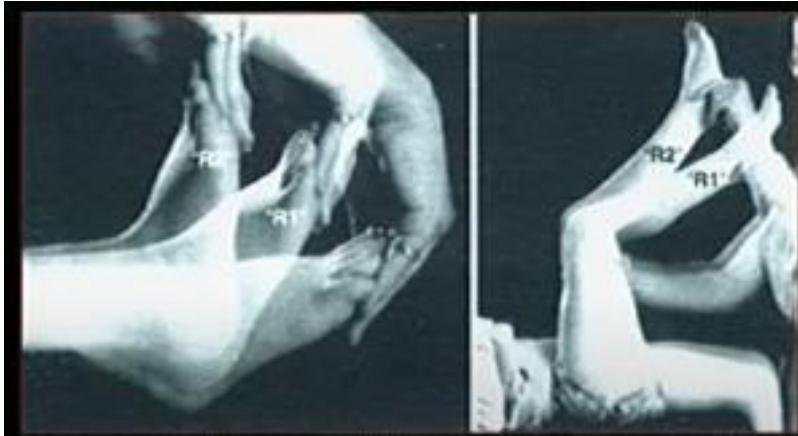


Figure 7-1 Modified Tardieu Scale (MTS) reproduced with permission Boyd (2022)
R1 is the quick stretch and represents the 'dynamic catch' in the muscle
R2 is the slow stretch representing available muscle range of motion

As this was a pragmatic clinical study, a number of different muscle groups were selected for BoNT-A injection based on individual clinical indicators. This resulted in a heterogeneous group of injected muscles within the study, reflecting realistic clinical practice (see Table 5-3).

For the purpose of analysis, change in R1, was used to record change in dynamic tone for gastrocnemius and hamstring muscles. As the most frequently injected muscles, these two muscle groups were considered representative of a change in spasticity for the sample (Table 5-5). A number of children received bilateral injections and the data of both limbs were included in the statistical analysis with corrections made for multiple comparisons, 52 children had gastrocnemius injected (n=73 muscles) and 25 children had hamstrings injected (n= 43 muscles).

Suggested clinical significance was determined for this study as a change larger than the published established standard error of measurement (SEM), ≥ 5 degrees in the gastrocnemius muscle (McDowell et al., 2000) and ≥ 10 degrees in the hamstring muscle (Fosang et al., 2003). The inclusion of less frequently injected muscles rendered meaningful statistical analysis impossible due to their small sample size. Only one child had neither of these muscles injected (having gracilis muscle injection only) and whilst excluded from this particular analysis for R1, was included

in all remaining analyses, including the more global measure of tone reduction ‘technical response’ presented later in the chapter (7.3.1).

A supplementary measurement of spasticity Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987), was also used in this study and univariate change scores for gastrocnemius and hamstrings are presented in Table 7-1. MAS scores in this study used an ordinal 6-point scale (0,1,1+,2,3,4), with 1+ replaced by 2 during subsequent analysis (0,1,2,3,4,5) in order to enable univariate statistical analysis. This method is in keeping with other research in the field (Kelly et al., 2019, Yap et al., 2010)

7.2.1.1 Modified Tardieu Scale (MTS) R1

A one-way repeated measures ANOVA was conducted with post hoc analysis using a Bonferroni adjustment to determine whether there was a statistically significant difference in outcome scores between baseline R1 (T0) pre-injection and at the three assessment time points post injection (T1-T3).

Change scores from baseline are presented in Table 7-2, together with an indication of their suggested clinical and statistical significance.

	Mean change R1 (°)			ANOVA
	[95% Confidence Interval]			
	T1	T2	T3	
Gastrocnemius (n=59)	-5.93** ^a [-9.53,-2.34]	-1.70 [-5.23,1.84]	-2.83 [-5.91,0.25]	F (3,174)=8.35, p<.001, partial η ² =.126
Hamstrings (n=37)	-17.30** ^a [-23.60,-11.00]	- 9.67* [-16.71,-2.64]	-10.84** ^a [-17.09,-4.60]	F(3,108)=17.08, p<.001 partial η ² =.322

**p<.001 *p<.01 ^a clinically significant change>SEM

Table 7-2 Mean change in R1 Hamstrings and Gastrocnemius muscles

Gastrocnemius MTS R1

Dynamic catch (R1) in the gastrocnemius muscle was measured in degrees as per the standardised testing protocol (see 4.2.2 and study manual Appendix 14.3).

As can be seen in Figure 7-2, dynamic muscle tone was reduced in the injected gastrocnemius muscles following BoNT-A injections at all post injection assessment time points (T1-T3) in comparison to baseline. However, this improvement in R1 only reached a statistical and clinically significant reduction in spasticity ($\geq 5^\circ$) in comparison to baseline score at 6 weeks ($p < .001$), and the change from baseline was no longer significant at 6 and 12 months.

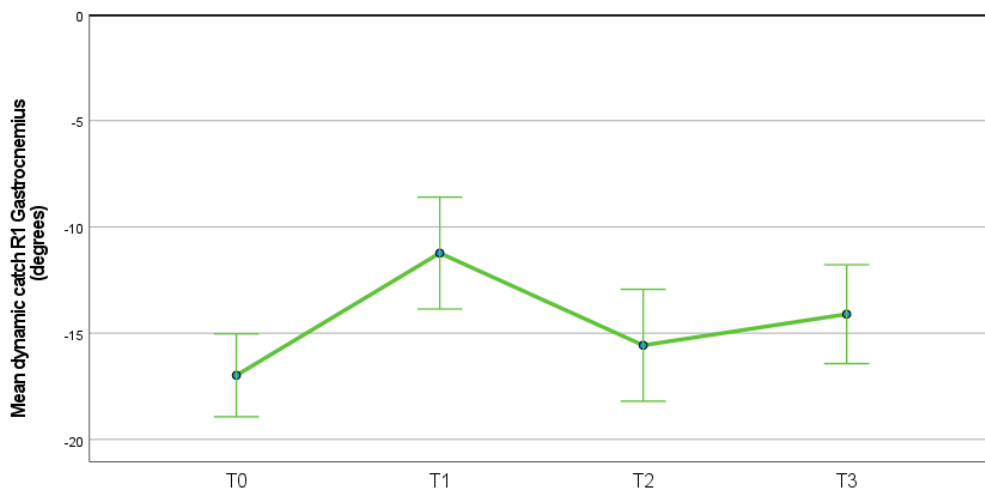


Figure 7-2 Mean change in dynamic catch R1 Gastrocnemius (n=59). Improvement in dynamic catch (R1) only reached a statistical and clinically significant reduction in spasticity ($\geq 5^\circ$) in comparison to baseline score at 6 weeks ($p < .001$)

This result was also mirrored by a significant reduction in spasticity as measured by the additional clinical measurement of spasticity MAS at T1 ($p < .001$), once again demonstrating a clinically significant improvement of ≥ 1 point change score at 6 weeks post injection which was no longer apparent at 6 and 12 months (Table 7-1)

Data up until T2 represented a single injection episode for the total sample.

However, by T3 (12 months), 20 children with gastrocnemius injections had been

re-injected (28 gastrocnemius muscles) compared to 32 children with a single injection episode (39 gastrocnemius muscles). Figure 7-3 shows the difference in R1 between the two groups

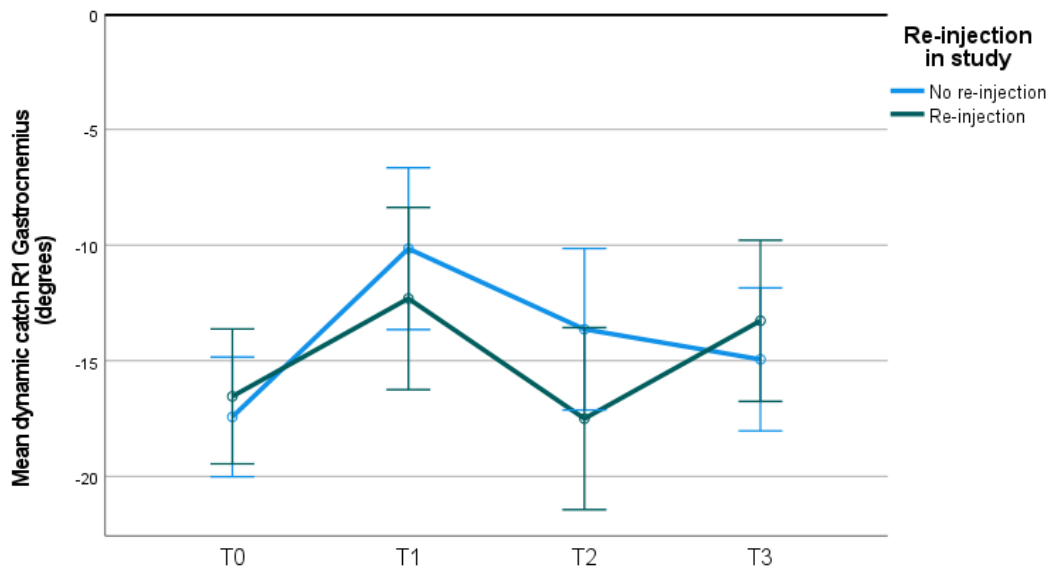


Figure 7-3 Mean dynamic catch R1 in Gastrocnemius by re-injection status. There was no statistically significant difference between the groups at any time point, including T2 (p=.36)

As can be seen the response differed between the two groups (re-injected and not re-injected within the study). However, further analysis with a Mann-Whitney U test revealed no statistically significant difference in R1 between the two groups at any time point including T2 (U=462.0,z=-1.239,p=.215) or T3 (U=474.5,z=-.924,p=.355). This is in keeping with other studies where more frequent injections did not result in improved outcome (Hastings-Ison et al., 2016). It is interesting to observe that no significant difference was seen at T2, the clinical assessment time point when decisions are made about the need for re-injection.

Hamstrings MTS R1

The dynamic catch (R1) in the hamstring muscle was also measured in degrees as per the standardised testing protocol (see 4.2.2 and study manual Appendix 14.3).

Reduction in dynamic catch $\geq 10^\circ$ relative to baseline scores was considered to be a clinically significant improvement.

As can be seen in Figure 7-4, dynamic muscle tone was significantly reduced in the injected Hamstring muscles following BoNT-A injections at all post injection assessment time points (T1-T3) in comparison to baseline. Improvement in R1 reached a clinically significant reduction in spasticity ($\geq 10^\circ$) at 6-weeks ($p < .001$) and 12-months but improvement at 6-months did not suggest clinical significance (Figure 7-4).

Additionally, spasticity as assessed by MAS followed a similar trajectory with a statistically significant reduction in dynamic tone seen at all time points which unlike MTS R1, suggested clinical significance at 6-weeks (≥ 1 point change), which was maintained at both 6 and 12-months (Table 7-1).

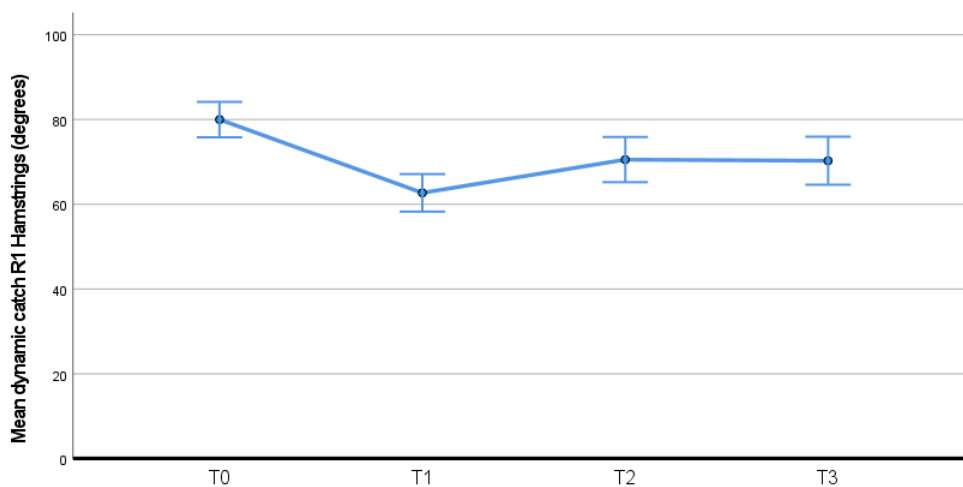


Figure 7-4 Mean dynamic catch (R1) in Hamstrings.
There was a significant reduction in dynamic catch(R1) from baseline at T1 ($p < .001$), T2 ($p < .01$) and T3 ($p < .001$)

Although the data up until T2 represented a single injection episode for the whole sample, by T3 at 12 months, 10 children had received a further injection cycle (representing 16 hamstring muscles) and 17 children (representing 27 hamstring muscles) had only received a single injection cycle. Children who had re-injection

showed a consistently lower dynamic catch at T1-T3. In contrast to gastrocnemius muscle injections, at T3 there was a difference between the two groups, with lower R1 scores (reduced spasticity) in re-injected hamstring muscles than those with no re-injection (Figure 7-5). A Mann-Whitney U test revealed this difference to be statistically significant difference ($U=77.50$, $z=-3.06$, $p=.002$), with significantly greater improvement in R1 for muscles re-injected ($61.3^\circ \pm 13.84^\circ$) in comparison to those with a single injection cycle ($78.70^\circ \pm 16.32^\circ$).

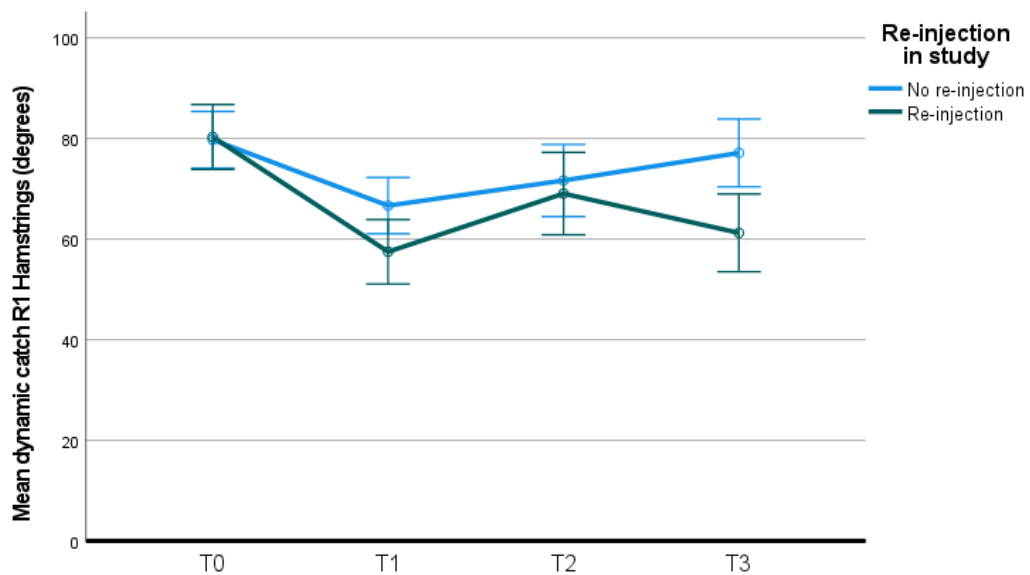


Figure 7-5 Mean dynamic catch (R1) in Hamstring muscles by re-injection status

Children who had re-injection in the study had significantly greater reduction in spasticity at T3 than those who had a single injection ($p=.002$). However, there was no significant difference in R1 between the two groups at any other time point

Those muscles which were not re-injected had significantly less improvement in dynamic catch at T1 ($U=110.00$, $z=-2.69$, $p=.007$) whilst at T2, the difference in R1 between the two groups was not significant. This highlights the complexity of selecting children for retreatment, decisions appear to be multifaceted and based on clinical need, and not the results of a single outcome. This could be based on a good response at 6 weeks assessment and evidence of increasing dynamic catch representing a return of spasticity at 6 months. Whereas the other group of children who had less response to BoNT-A also had less marked return of spasticity and therefore re-injection may not have been indicated at that time.

7.2.2 Muscle selectivity- Selective Motor Control scale (SMC)

Muscle selectivity (an indicator of motor control) was evaluated by SMC in the study as described in Chapter 4 (4.2.2). SMC scores (0-4) were assessed for each injected limb (n=90). A higher score (maximum 4) represents greater muscle selectivity.

Since the SMC scale represents data on an ordinal level, non-parametric statistical tests were used. Descriptive data are presented as median and interquartile range in Table 7-1. A Friedman's test was conducted and there was a significant effect for time ($X^2(3), 34.01, p < .001$), with SMC scores improved from baseline at all post injection time points (Figure 7-6). Post hoc analysis with a Bonferroni correction for multiple comparisons revealed SMC scores were significantly improved from baseline at 6- and 12-months post injection ($p = .021, p = .003$). However, as illustrated in Figure 7-6, there were a number of outliers at T1 and the improvement at 6 weeks was not found to be significantly improved ($p = .10$) from baseline scores. Analysis with a Mann Whitney U test showed no significant difference in SMC scores ($p > .05$) at any time point between the muscles that had been re-injected and those which had a single injection episode during the study.

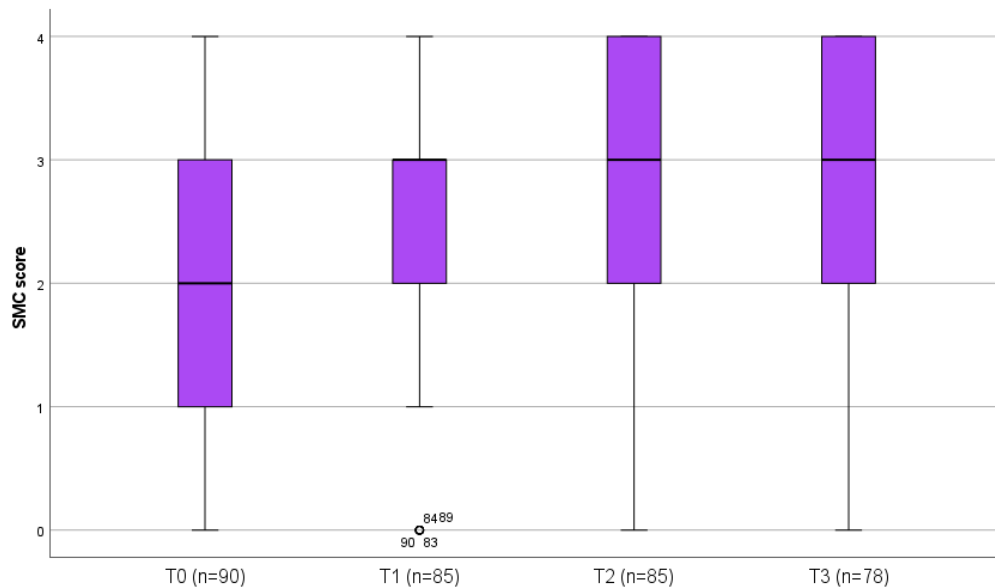


Figure 7-6 Boxplot showing Median SMC scores over 12 months and 25th and 75th centiles (n=70)

It has been suggested that a change score of 1 point is clinically meaningful and an SMC score of ≥ 3 has been associated with improved gait parameters (Boyd and Graham, 1999). Within this study SMC scores showed an improvement in median score of 1 point from baseline, suggesting a clinically significant improvement at 6 weeks which was maintained throughout 12 months. However, in the absence of published MCIDs it is hard to interpret the true clinical significance of these results.

7.2.3 Pain - modified Faces Pain Scale (mFPS)

Pain was measured using the modified Faces Pain Scale, measured on a 10-point scale, and with the pain and impact of disability domain of the CPQOL, measured as a percentage score. A lowering of both pain scores represents improvement, only the mFPS has published clinical significance values, with change scores in the mFPS of ≥ 1 considered the MDC and ≥ 2 suggested as the MCID (Tsze et al., 2015).

Statistical analysis with a one-way repeated measures ANOVA suggested there was a statistically significant difference in pain scores across the time points ($p=.001$), (Figure 7-7). As the assumption of sphericity by Mauchly's test was not met ($p<0.05$) a Greenhouse Geisser correction was applied, $F(3,128.2)=6.46$, $p=.001$ partial $\eta^2=.116$.

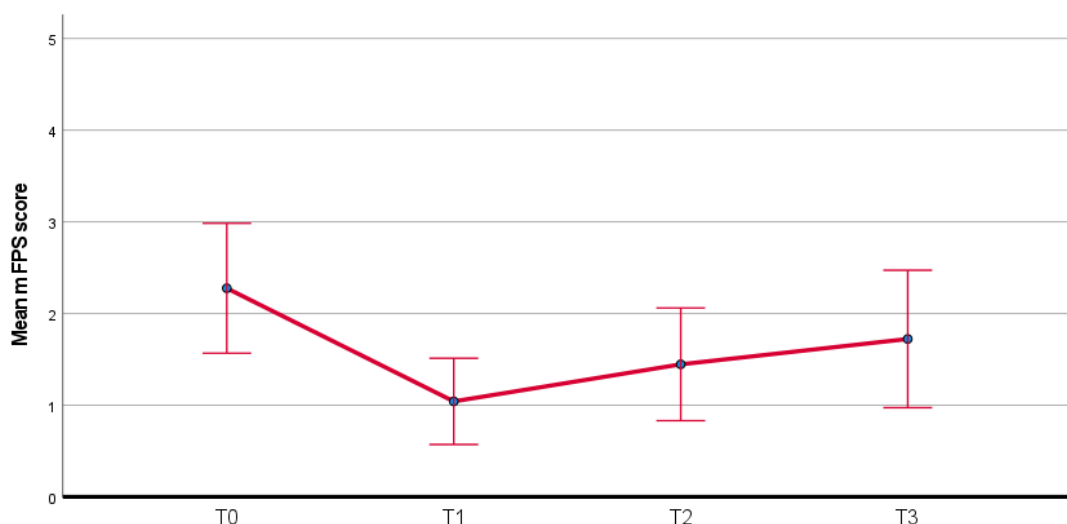


Figure 7-7 Mean m FPS Pain scores over 12 months (n=47).

There was a significant improvement (reduction) in pain scores at T1 ($p<.001$) and T2 ($p=.44$) but this reduction in scores from baseline was not significant at T3

Post hoc analysis with a Bonferroni adjustment revealed a statistically significant reduction in pain scores between baseline (pre-injection) and six weeks post injection at T1 ($p < .001$) and six months post injection, T2 ($p = 0.44$), however the difference in scores from baseline was no longer statistically significant at T3. Baseline reported pain scores were generally low for the whole sample as can be seen in Table 7-1, and less than 50% of children reported pain at any assessment time point.

Although the scores were statistically significantly different at T1 and T2 they exceeded MDC only at T1 and did not reach the clinical significance of ≥ 2 point MCID at any time point (Tsze et al., 2015).

Pain scores as reflected by CPQOL also followed a similar trajectory and were significantly reduced at both six weeks by 7% ($p < .001$) and six months by 6% ($p < .01$) but the reduction in pain score was also no longer significant at twelve months (Table 7-1). In the absence of MCIDs for CPQOL it is difficult to comment on the clinical significance of the improvement seen in CPQOL Pain scores in this study.

Summary of outcomes in the Body Structure and Function ICF domain

- Short term reduction in spasticity (R1) was seen in both gastrocnemius and hamstring muscles at 6 weeks (T1) and this reached both statistical and clinical significance.
- Longer term improvement in R1 was seen in the hamstring muscles beyond 6 months (T2 and T3). The reduction in spasticity as measured by R1 remained significant at all time points in comparison to baseline. This approached clinical significance at T2 and reached clinical significance at T3.
- MAS scores statistically mirrored those of MTS R1 results for both hamstrings and gastrocnemius muscles and suggested a clinically significant reduction in spasticity at 6 weeks post injection for gastrocnemius muscles and throughout 12 months for hamstring muscles.
- SMC scores were significantly improved between baseline at 6 and 12 months but the improvement did not reach statistical significance at 6 weeks post injection (T1).
- Pain scores (mFPS and CPQOL) were significantly improved following BoNT-A injections at 6 weeks and 6 months, but the clinical significance of these scores is uncertain.

7.3 Responders vs non responders for the study

As this was a pragmatic clinical study, a number of different muscles were selected for injection and both unilateral and bilateral injections were administered. Within BoNT-A research, it is increasingly being recognised that a global assessment of general response to BoNT-A may more accurately reflect the heterogeneity of clinical practice (Heinen et al., 2021, Löwing et al., 2017).

Introducing a global score of reduction in dynamic tone permits an analysis of a general response to BoNT-A, allowing comparison of individuals with different treatment regimens, and moving away from an overemphasis of change at an individual muscle level for what is frequently such a widely diverse group. A global measure of 'technical response' in the muscle following BoNT-A treatment has previously been reported by Alexander et al. (2018), who in their study following gastrocnemius injections described this as a reduction in dynamic catch as detected by $MTS \geq 5^\circ$.

Technical response (TR) was also reported within this study, and was defined as a change in dynamic muscle length as measured by MTS R1 (Figure 7-1), exceeding the standard error of measurement (SEM) of the injected muscle. This was identified as $\geq 10^\circ$ for those children who had Hamstring muscles injected and $\geq 5^\circ$ for children with Gastrocnemius or Gracilis muscle injections (Fosang et al., 2003, McDowell et al., 2000).

The 'technical response' to BoNT-A injections was determined initially at the first clinical assessment T1, at 6 weeks post injection. T1 was selected as a clinically recognised time frame when a reduction in dynamic tone (spasticity) could be expected following treatment (Boyd and Graham, 1999).

Technical response (TR) was classified from the gastrocnemius muscle for the 52 (81%) children in the study who had gastrocnemius muscles injected (21 children had these injected bilaterally). Of the remaining 12 children without gastrocnemius injections, 11 children had hamstring muscles injected (10 children bilaterally) and one child had gracilis muscles injected (bilaterally). TR was therefore determined from Hamstrings and Gracilis muscles for these children respectively.

At T1, a child's response to BoNT-A was evaluated relative to a change beyond the SEM for the muscle injected ($\geq 10^\circ$ for hamstrings and $\geq 5^\circ$ for gastrocnemius and gracilis), and was determined in one of three ways:

😊 **Responder:** (technical response) Improvement in dynamic catch R1 as shown by a *reduction* in the R1 angle of the injected muscle \geq SEM for muscle injected.

😐 **Non-responder:** (no technical response) Dynamic catch R1 unchanged or R1 angle *reduced* $<$ SEM for muscle injected

😞 **Deterioration:** Dynamic catch deteriorated, R1 angle *increased* $>$ SEM for the muscle injected

Bilateral injections

With bilateral injections, a technical response in the muscle was recorded as a responder if improvement in dynamic catch R1 was \geq SEM in one limb *without* deterioration of the other side. To reflect the complexity of rating technical response following bilateral injections, an algorithm of response was defined for the study and is summarised in Table 7-3.

At T1 a child's response to BoNT-A following bilateral injections was determined as responder, non-responder or deteriorator as highlighted below.
















Technical Response for Bilateral Injections				
	Technical response in both limbs <i>or</i> Technical response in one limb and no technical response in the other limb	 	 	Responder
	No Technical response in either limb <i>or</i> Technical response in one limb and deterioration in the other limb	 	 	Non Responder
	Deterioration in both limbs <i>or</i> No technical response in one limb and deterioration in the other limb	 	 	Deteriorator

Table 7-3 Definition of Technical Response for bilateral injections

7.3.1 Technical response – Results

It has been suggested that reporting *‘the proportion of patients achieving a degree of improvement beyond measurement error can often be a more informative method for describing the effects of the intervention than overall mean change’* (Haley and Fragala-Pinkham, 2006). Therefore, the technical responses within the study were summarised using percentage scores.

At T1 45 children (75%), showed a technical response in the muscle following BoNT-A treatment (a reduction in the dynamic catch as measured by R1 at T1),

9 children (15%) did not show a technical response (dynamic catch did not improve) and 6 children (10%) showed a deterioration as dynamic catch had increased when compared to baseline R1 measurement.

Whilst response at six weeks classified any short-term technical response in the muscle, from a clinical perspective it was important to see how the technical response changed at each subsequent assessment time point for the whole group over 12 months. Technical response was then evaluated across the 12 months (Figure 7-8).

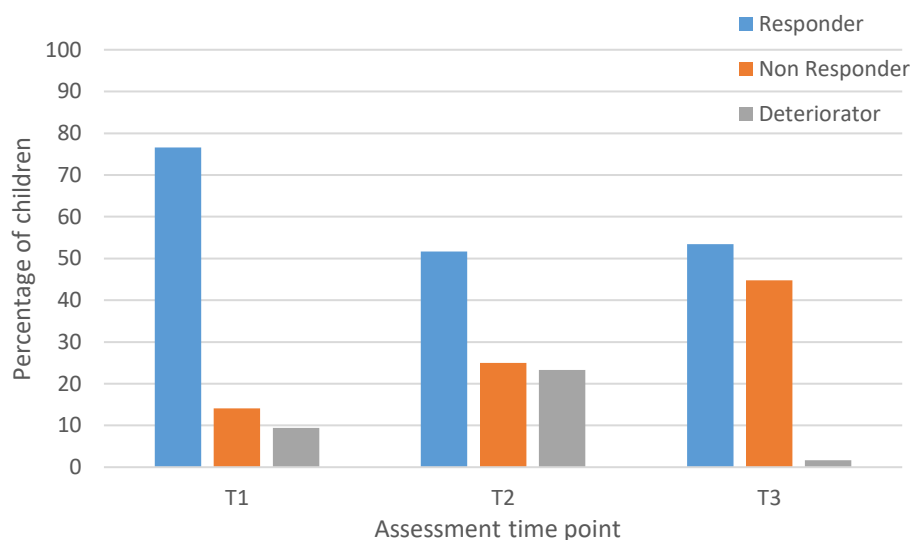


Figure 7-8 Technical response over 12 months following BoNT-A injections

This graph demonstrates the percentage of children classified as showing a technical response to BoNT-A treatment across 12 months: 75% at T1, 51.7% at T2 and 53.4% at T3 (45.2 % of these followed a single injection episode)

At T2 6 months post injection, 51.7% of the children assessed showed a technical response, 23.3% children were classified as no technical response and 25% had deteriorated in comparison to baseline scores. The reduction in responders and increase in children who had deteriorated could have been a driver for re-injection.

By T3 at 12 months, 53.4 % of children assessed were classified as having a technical response (45.2% of these responders had a single injection and 54.8% had undergone re-injection within the study). 44.8% of children were classified as having no technical response and one child (1.8%) was classified as having deteriorated in comparison to baseline.

Re-injection

A Mann-Whitney U test was run to determine any difference in technical response (TR) following BoNT-A (T1, T2 and T3), between the two groups of children, those requiring re-injection between 6 and 12 months of the study and those receiving a single injection episode.

Distributions of Technical response for the two groups, were similar, as assessed by visual inspection. Technical response status was not statistically significantly different between the groups at 6 weeks, or 6 months post injection but was significantly different at T3 ($U=532.5, z=2.258, p = .024$).

At T3 as expected, the percentage of children classified as responders in the re-injected group was higher (70.8%) than those classified as responders in the single injection group (41.2%) (Figure 7-9).

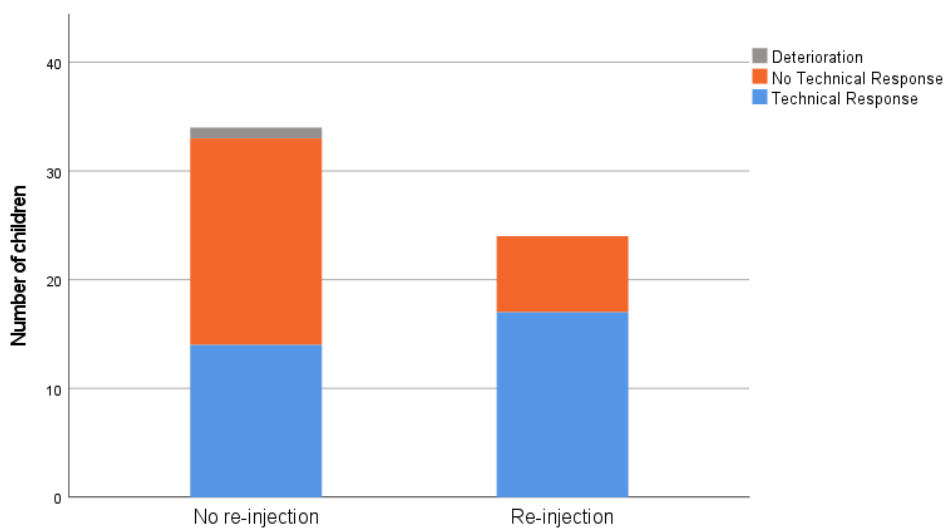


Figure 7-9 Technical response at T3 comparing single versus re-injection groups

Although the children showed a difference in technical response in the muscle at T3, re-injection status did not appear to be significantly associated with any change in quality of movement as measured by QFM (6.1), activity (7.4) or participation scores (7.5).

The lack of a significant difference in TR between the groups at six months (T2) is pertinent as this is the clinical time point when decisions are made about the need for re-injection. The clinical decision-making process within this study did not appear to be related to changes in spasticity alone. This was highlighted by the re-injection of 39% of children who had been identified as 'responders' at T2, and 26.7% of those children classified as 'non responders', and 57.1% of children who were classified as 'deteriorated' following the first injection episode in the study.

This underlines the complex multi-faceted decision making involved within the clinical setting when selecting children for re-injection, which does not appear to be based on evaluation of a single outcome.

7.4 Activity

Three standardised validated outcome measures were used in the study to evaluate change in activity following BoNT-A injections over the twelve-month period (administration details for the measures can be found in 14.3). The activity measures were:

- One Minute Fast Walk Test (1MFWT) which evaluates walking ability and endurance and is measured in metres (greater distance measured in metres represents improvement)
- Modified Timed Up and Go Test (mTUG) which evaluates mobility and functional balance (reduced time to complete the test, measured in seconds, represents improvement)
- Gross Motor Function Measure (GMFM-66) which evaluates gross motor function in two dimensions of the GMFM, D: standing and E: walking, running, and jumping dimensions (higher percentage scores represent an improvement in gross motor function).

One-way repeated measures ANOVAs were conducted to determine any statistically significant differences in outcome measures over the course of 12 months. In order to assess the clinical significance of the results, the results have been related to published MCIDs whenever possible.

Descriptive and inferential statistics for the three activity measures are summarised in Table 7-4. As with the QFM attribute data, due to the differing levels of motor abilities within the GMFCS levels I-III the activity scores as captured by the three tests differed, particularly with regards to children in GMFCS level III. A subgroup analysis was performed, and the data were stratified by GMFCS levels which, due to the small sample size (<20 per group), were analysed using non-parametric tests in order to identify change at individual GMFCS levels. This permitted comparison with published MCIDs.

Activity Measure	Baseline T0 n=64	T1 6 weeks n=58	T2 6 months n=60	T3 12 months n=57	P (effect of time) n=48
TUG (s) Mean (SD) (% change from baseline)	11.90 (16.84)	11.13 (12.98) (6.5%)	10.2 (12.8) ^a (14%)	8.24 (10.47) ^a (31%)	F(3,141)=1.94, p=.17 (partial η ² =.04)‡
1 MFWT (m) Mean (SD) (% change from baseline)	62.92 (23.39)	65.95 (24.40) (5%)	64.77 (24.52) (3%)	71.07 (24.23) ^a (13%)	F(3,141)=2.17, p=.094 (partial η ² =.04)
GMFM-66 (%) Mean (SD) (% change from baseline)	71.79 (13.78)	73.69 (14.49) ^{*** a} (1.9%)	74.68 (14.33) ^{*** a} (2.89%)	78.13 (14.29) ^{*** b} (6.34%)	F(3,141)=34.32, p<.001 (partial η ² =.42)

***p<0.001 ** p<.0.01 *p<.05 following Bonferroni post hoc test for multiple comparisons clinically significant change>MCID
^a moderate effect size (0.5) ^b large effect size (0.8)‡ Greenhouse-Geisser correction

Table 7-4 Activity outcome measures

7.4.1 TUG scores

A one-way repeated measures ANOVA was conducted to see if there was a statistically significant difference in TUG scores over the 12 months post BoNT-A. Although scores improved from baseline to each post injection time point (Figure 7-10), these improvements were not found to be statistically significant (p=.17). However, change scores were found to be clinically significant at T2 and T3 with medium effect size when compared to published MCID values (≥1.2 seconds

(Hassani et al., 2014)

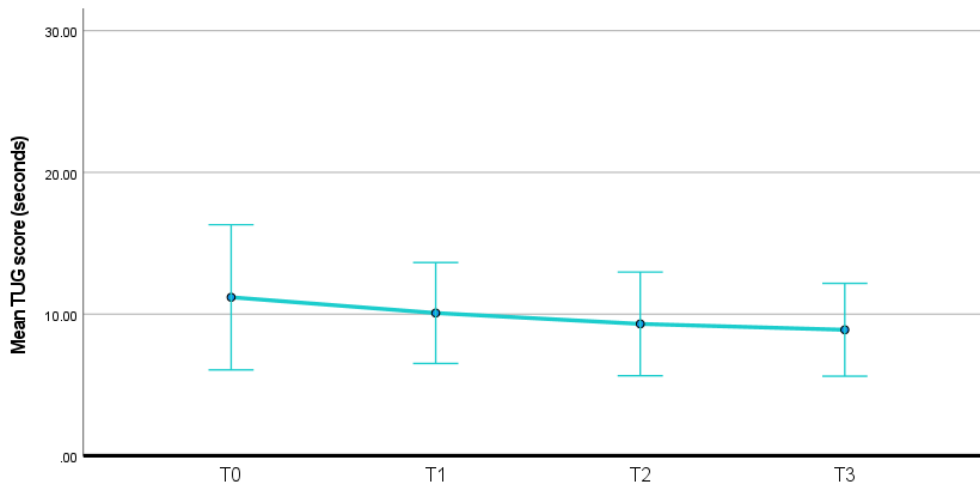


Figure 7-10 Mean TUG score all GMFCS levels across 12 months (n=48).

The improvement in scores from baseline were not found to be statistically significant ($p=.17$).

Sub-group analysis demonstrated markedly slower TUG scores in GMFCS level III children than children in GMFCS levels I and II (Figure 7-11). There was a statistically significant improvement in TUG scores from baseline at all post injection time points for GMFCS I and GMFCS II children, but this was not found to be significant for children in GMFCS level III. Details regarding mean TUG scores per GMFCS level are summarised in Table 7-5. Post-hoc analysis for both GMFCS levels I and II revealed that TUG scores were significantly reduced at T2 and T3 in comparison to baseline scores but not at T1. Mean change scores also appeared to be clinically significant, exceeding published MCID estimates for large effect size (0.36 seconds) in GMFCS I children and moderate effect size (0.54 seconds) in GMFCS II children (Carey et al., 2016).

The delay in response could be associated with increased weakness following BoNT-A and the time required to translate reduced tone into improved functional ability. This was in keeping with a delay in clinically significant improvement in QFM attributes of Dissociated Movement and Stability until 6 months post treatment. Children in GMFCS level III also exceeded MCID estimates for moderate effect size at T2 and T3 (3.32 seconds), suggesting clinical significance, but the results were not

statistically significantly different from baseline scores at any time point, suggesting a large variability in the scores.

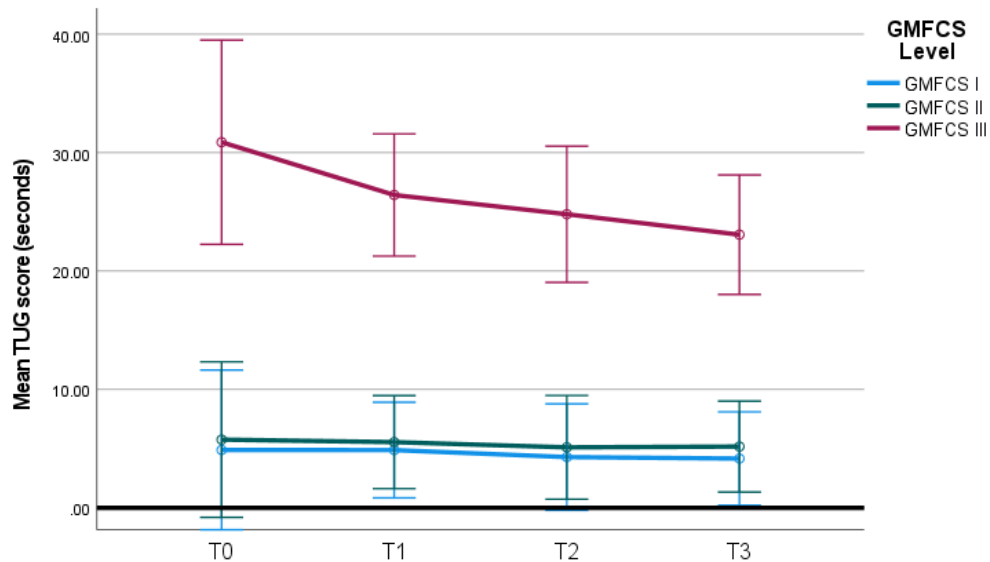


Figure 7-11 Mean TUG scores by GMFCS level.

Improvement in TUG scores were not significant for any GMFCS level at T1 but were significant at T2 and T3 for GMFCS Level I ($p < .001$) and II ($p < .01$)

TUG N Mean (SD) seconds	Baseline T0	6 weeks T1	6 months T2	12 months T3	Friedman Test $\chi^2(3)$
GMFCS I	5.00 (1.05) n=22	5.01 (1.10) n=21	4.36 (0.74)** ^b n=20	4.23 (0.85)** ^b n=21	19.48 p<.001
GMFCS II	5.77 (1.40) n=24	5.50 (1.47) n=20	4.99 (1.39) ^a n=23	4.98 (1.53) ^a n=23	11.32 p=.01
GMFCS III	28.51 (25.29) n=18	25.32 (17.12) n=17	24.12 (17.74) ^a n=17	20.48 (17.18) ^a n=13	6.14 p=.11

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ following Bonferroni post hoc test for multiple comparisons clinically significant change >MCID ^a moderate effect size (0.5) ^b large effect size (0.8)

Table 7-5 Mean TUG scores (seconds) by GMFCS level

7.4.2 1MFWT scores

Although the average distance walked improved from baseline at each post injection time point (Figure 7-12), this change was not found to be statistically significant ($p=0.94$). Mean change scores for the whole group are shown in (Table 7-4). Improvement at T3 suggested a clinically significant improvement from baseline score at T3 exceeding the MCID ($\geq 5.6\text{m}$) with a moderate effect size (Hassani et al., 2014). Although the lack of statistical significance suggests improvement was not consistent.

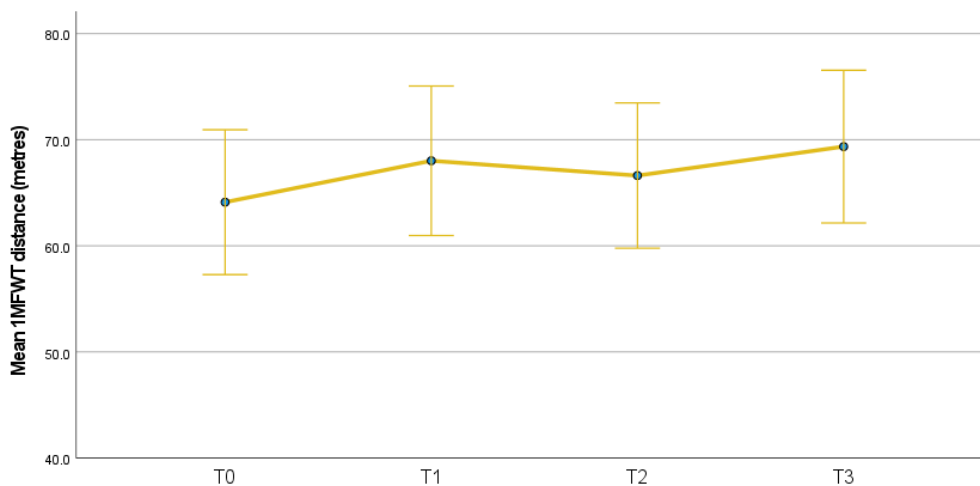


Figure 7-12 Mean 1MFWT distance walked all GMFCS levels over 12 months $n=48$. Improvement from baseline was not found to be significant at any time point ($p=.094$)

A significant difference in distance walked was observed between children in GMFCS level III and those in GMFCS I and II ($p<.001$) but not between GMFCS levels I and II (Figure 7-13). Further analysis revealed no significant improvement in distance walked for any individual GMFCS levels following BoNT-A injections (Table 7-6). However, mean change scores exceeded MCIDs, suggesting there may have been a clinically significant improvement at 12 months (T3) for children in GMFCS level I, 7.8 m (MCID 5.1m) and at 6 weeks (T1) for children in GMFCS Level II, 9.8 m (MCID 9.0 m). The lack of statistical significance once again suggested improvement was not consistent. Nevertheless, mean scores for GMFCS Levels in this study were in keeping with published data (Hassani et al., 2014).

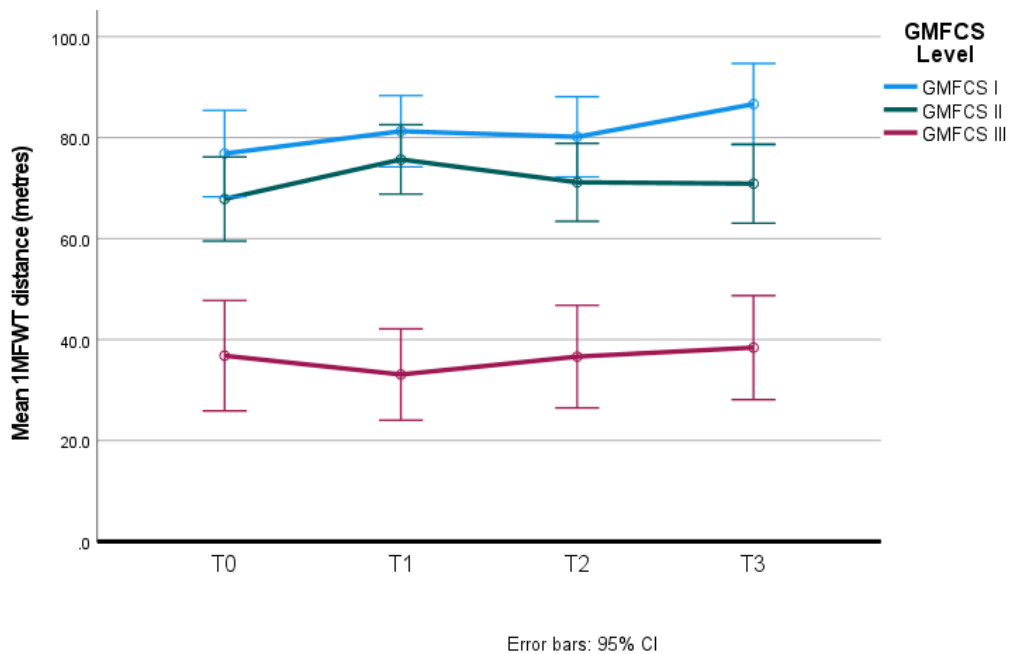


Figure 7-13 Mean 1 MFWT distance walked highlighted by GMFCS level
 The change from baseline score was not significant for any GMFCS level. The graph highlights the significant difference in distance walked between children in GMFCS level III and those in GMFCS I and II ($p < .001$) but distance walked was not significantly different between GMFCS levels I and II

1MFWT Mean (SD) seconds	Baseline T0	6 weeks T1	6 months T2	12 months T3	Friedman Test χ^2 (3)
GMFCS I n=18	78.65 (20.24)	81.28 (16.20) n=21	80.17 (13.06) n=20	86.64 (0.85) ^a n=21	6.02 p=.11
GMFCS II n=19	67.89 (15.06)	75.68 (15.42) ^b	71.16 (19.18)	70.90 (20.52)	7.24 p=.06
GMFCS III n=11	36.82 (18.86)	33.09 (11.04)	36.64 (17.44)	34.42 (8.80)	6.94 p=.07

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ following Bonferroni post hoc test for multiple comparisons clinically significant change > MCID ^a moderate effect size (0.5) ^b large effect size (0.8)

Table 7-6 1MFWT Mean distance walked (metres) by GMFCS level

7.4.3 GMFM -GMFM-66

There was a significant improvement in GMFM-66 scores from baseline to all time points ($p < .001$) following BoNT-A injections (Table 7-4). MCIDs established for change scores in GMFM-66 for GMFCS Levels I-III are 0.8% change for moderate effect size and 1.3 % change for large effect size (Wang and Yang, 2006). Results in this study suggested that change in mean GMFM scores illustrated in Figure 7-14 represented a clinically significant improvement exceeding MCID of moderate effect size at T1 and T2 and large effect size at T3 for the whole group analysis (Table 7-7).

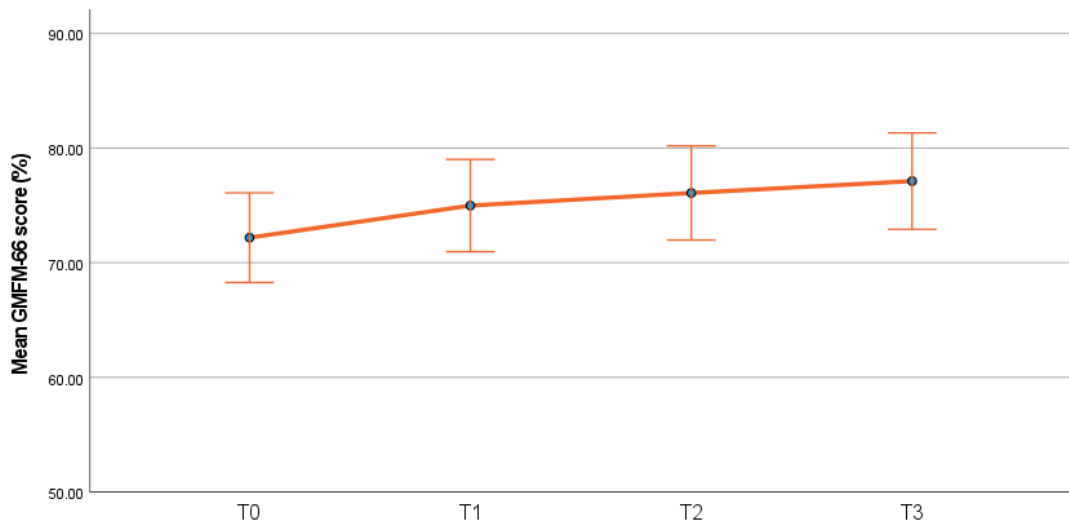


Figure 7-14 Mean GMFM-66 score all GMFCS levels n=48.

Significant improvement in score from baseline was seen at all time points ($p < .001$)

As with previous outcomes there was a marked difference in scores between the different GMFCS levels (Figure 7-15).

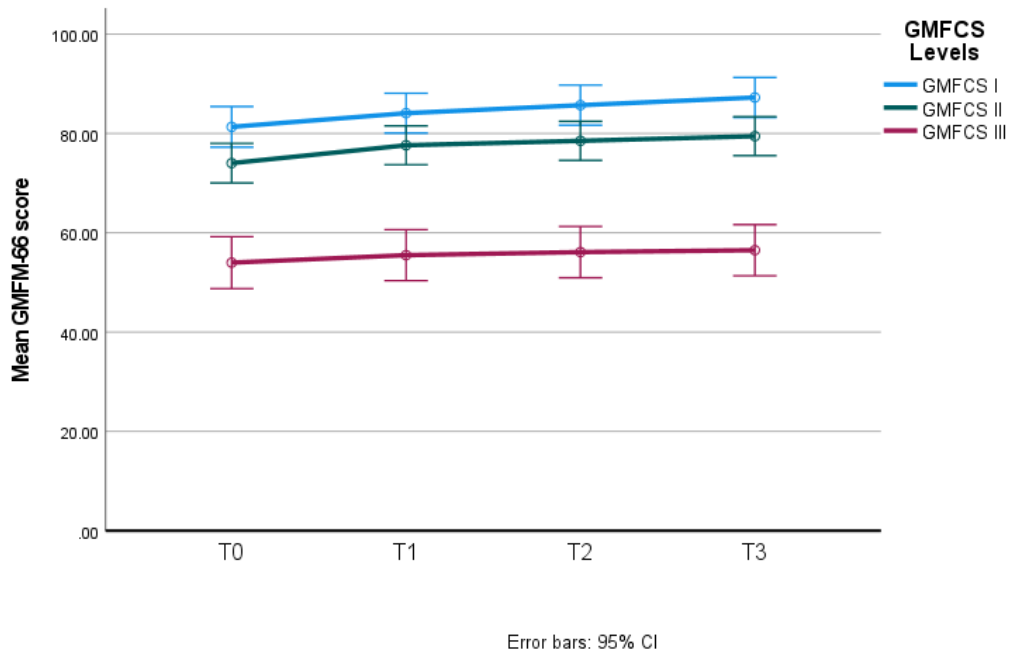


Figure 7-15 GMFM-66 scores by GMFCS level across 12 months n=48.
 Significant improvement in scores was seen for children in GMFCS II only at T1 ($p<.01$) and for all levels at T2 GMFCS I ($p<.05$) GMFCS II and III ($p<.001$) and at T3 GMFCS I and II ($p<.001$) and GMFCS III ($p<.01$)

Subgroup analysis was performed between the GMFCS levels using a Friedman test. The results confirmed a statistically significant difference in GMFM-66 scores ($p<.001$) across the four assessment time points for all GMFCS levels (Table 7-7). Pairwise comparisons were performed (SPSS Statistics,2012) with a Bonferroni correction for multiple comparisons.

GMFM-66 Mean % (SD)	Baseline T0	6 weeks T1	6 months T2	12 months T3	Friedman Test χ^2 (3)
GMFCS I	80.98 (9.42) n=22	83.09 (9.20) ^a n=21	85.10 (9.58) ^{*b} n=20	87.16 (8.22) ^{***b} n=21	27.91 $p<.001$ n=18
GMFCS II	75.70 (9.85) n=24	78.76 (9.73) ^{***b} n=20	78.87 (9.05) ^{**b} n=23	81.37 (10.16) ^{***b} n=23	23.22 $p<.001$ n=19
GMFCS III	55.37 (6.81) n=18	56.14 (7.38) ^a n=17	56.77 (5.79) ^{**b} n=17	57.81 (6.41) ^{***b} n=13	18.42 $p<.001$ n=11

*** $p<.001$ ** $p<.01$ * $p<.05$ following Bonferroni post hoc test for multiple comparisons /clinically significant change>MCID ^a moderate effect size (0.5) ^b large effect size (0.8)

Table 7-7 Mean GMFM-66 scores for total sample by GMFCS level

GMFM-66 scores were improved significantly from baseline only for children in GMFCS level II at T1, six weeks post injection ($p < 0.001$) and for children in all GMFCS levels, I, II and III at six months and 12 months post injection ($p < 0.001$ - $p < 0.5$). However, improvement in mean change scores at all time points post injection suggested clinically significant improvements in gross motor function in excess of published MCIDs for children in all GMFCS levels I, II and III (Oeffinger et al., 2008). However, the absence of statistical significance suggests that the improvement was not consistent. Mean scores for GMFCS levels are in keeping with the work of others in the field (Smits et al., 2010).

Summary of Activity outcomes

TUG

- Although mean change scores exceeded MCIDs at 6 and 12 months for the whole group (GMFCS I-III), there were no statistically significant improvements in functional balance as measured by TUG in comparison to baseline post BoNT-A injections.
- Subgroup analysis revealed statistically significant improvement in TUG scores for GMFCS Levels I and II but not children in GMFCS Level III between baseline and 6- and 12-months post injection. These changes exceeded MCIDs suggesting a clinically significant improvement.

1MFWT

- Walking capacity was not statistically significantly improved on univariate analysis for the whole sample or individual GMFCS levels following BoNT-A injections.
Subgroup analysis revealed no significant improvement in gait parameters following BoNT-A for any GMFCS group. Although changes exceeded MCIDs for children in GMFCS level II children at 6 weeks and GMFCS Level I children at 12 months.

GMFM-66

- There was a statistically significant improvement in gross motor function following BoNT-A. Mean GMFM-66 scores increased for the whole group at all post injection time points in comparison to baseline, these exceeded MCIDs suggesting a clinically significant improvement for the total group post injection at T1-T3.
- Subgroup analysis of GMFM-66 scores demonstrated that children in GMFCS Level II showed a statistically significant improvement from baseline at all-time points, whilst children from GMFCS levels I and III showed significant improvement only at T2 and T3. Mean change scores exceeded MCIDs at all time points suggesting a clinically significant improvement in children from all GMFCS levels post BoNT-A injections at T2 and T3 and for children in GMFCS Level II at T1.

7.5 Participation outcome measures

Participation and quality of life data were collected across all four time points (T0-T3) via two questionnaires: Cerebral Palsy Quality of Life Measure (CPQOL) and Participation Environment Measure -Child and Youth (PEM-CY). Both of these questionnaires were completed by parents who were strongly encouraged to involve their child in the scoring whenever possible.

Health Related Quality of Life (HRQoL)

One of the main challenges of measuring paediatric HRQoL is that proxy assessment may be necessary (Otero et al., 2013) The parent reported version of CPQOL was used throughout the study. It was decided *a priori* to use the proxy measure of CPQOL reporting in order to ensure uniformity in scoring for all participants. Evidence has shown that independent reporting for CPQOL has not been considered reliable in children younger than nine years old and the self-reported version is only validated for use by children from nine years of age (Waters et al., 2006). As anticipated the majority of the children in the study were younger than nine years old and 48% had some form of learning disability, making self-reporting difficult. However, recognising the limitations of proxy measures when reporting HRQoL, all families were encouraged where possible to complete questionnaires in discussion with their children, to ensure the voice of the child was heard (Mpundu-Kaambwa et al., 2021).

In order to answer the question regarding HRQoL specifically related to feelings about function and participation, two domains were used from the CPQOL; feelings about functioning (Function) and participation and physical health (Participation). Results for the pain and disability domain of CPQOL were included in the previous section (7.2.3).

Participation

Participation was measured by a parent reported PEM-CY questionnaire. Participation is a complex, multifaceted construct and it has long been recognised that there are two components of participation as defined by the ICF “attending *and* being involved in life situations” (WHO, 2007). Therefore, two domains of the

PEM-CY were selected for evaluation: *Average frequency* of participation in activities, which reflects both the attendance and range of activities that a child is involved with and *Average involvement* in these activities which reflects the experience of a child's participation whilst carrying out these activities. Average frequency and Average involvement were measured in all three settings: home, school and community. These key functional activity and participation domains from the outcome measures were considered the most reflective of level of participation for the study and descriptive statistics and results from statistical tests have been summarised in Table 7-8.

Variable (%)	Baseline (T0) Mean (SD)	6 weeks (T1) Mean (SD)	6 months (T2) Mean (SD)	12 months (T3) Mean (SD)	P main effect of time	N
CPQOL						
CPQOL Function (%)	67.48 (14.34) n=64	73.92 (12.61)*** n=60	72.88 (11.96)* n=60	72.78 (12.64) n=57	F(3,144)=6.79 p<.001	49
CPQOL Participation (%)	56.72 (18.34) n=64	64.22 (16.23)* n=60	65.10 (15.23)** n=60	64.70 (14.92)** n=57	F(3,144)=7.00 p<.001	49
PEM-CY						
Home Frequency (0-7)	5.38 (0.92) n=64	5.68 (0.80)** n=58	5.75 (0.74)** n=59	5.72 (0.76)* n=55	F(3,138)=7.36 p<.001	47
Home Involvement (1-5)	3.89 (0.53) n=64	4.13 (0.53)** n=58	4.16 (0.51)*** n=59	4.12 (0.65) n=55	F(3,138)=5.74 p=0.003	47
School Frequency (0-7)	3.78 (1.73) n=63 ^β	3.97 (1.11) n=57	4.21 (1.09)* n=58	4.10 (1.14) n=54	F(3,135)=3.11 p=0.03 [¥]	46
School Involvement (1-5)	3.94 (0.83) n=63	3.97 (1.11) n=57	4.21 (1.09)** n=58	4.10 (0.71) n=54	F(3,135)=4.02 p=0.015 [¥]	46
Community Frequency (0-7)	2.56 (0.97) n=64	2.85 (1.00) n=58	2.78 (0.95) n=59	2.90 (1.06) n=55	F(3,138)=2.25 p=0.09	47
Community Involvement (1-5)	4.06 (0.67) n=64	4.19 (0.62) n=58	4.00 (0.76) n=59	4.19 (0.62) n=55	F(3,138)=3.00 p=0.05 [¥]	47

Significant change from baseline ***p<0.001 ** p<.01 *p<.05 following Bonferroni post hoc test for multiple comparisons ¥ Greenhouse-Geisser correction β one child did not attend school N=Complete data sets for statistical analysis

Table 7-8 Participation scores descriptive statistics and statistical analysis

One-way repeated measures ANOVAs demonstrated statistically significant improvement in both CPQOL and PEM-CY scores following BoNT-A injections over a 12-month period. Post hoc analysis revealed that CPQOL scores for function and participation were significantly increased from baseline at both six weeks (T1) and six months (T2) post injection. However at 12 months (T3) only the CPQOL participation scores remained significantly increased in comparison to baseline scores.

In the absence of published MCIDs for CPQOL it is challenging to evaluate the true clinical significance of these change scores. However, change scores >5% have been reported as significant in other studies using CPQOL as an outcome measure following surgical intervention (selective dorsal rhizotomy) (Pennington et al., 2020). Change scores exceeded 5% for both CPQOL participation and function at all post injection assessments suggesting a clinically significant improvement following BoNT-A treatment.

The average frequency of participation in home activities as measured by PEM-CY were significantly improved for children at home at six weeks, six months and twelve months post injection in comparison to the average baseline scores. In addition there was also a significant improvement in involvement in participation in home activities at six weeks and six months post injection but this improvement was no longer significant at 12 months.

Participation in school activities (both in average frequency of activities and involvement in activities) was significantly improved at six months post injection in comparison to baseline scores. However, children did not demonstrate any significant improvement in participation in community activities (frequency or involvement) at any time point. Change scores were small with improvement in average frequency in the three settings ranging from 0.19-0.43 and average involvement 0.03-0.27. In the absence of MCIDs it is difficult to interpret the clinical significance of these changes post BoNT-A treatment.

Summary

CPQOL

- Children's wellbeing regarding their *feelings about functioning* in activities was significantly improved in comparison to baseline pre-injection scores at 6 weeks and 6 months post BoNT-A injections
- Children's wellbeing regarding *participation and their physical health* showed statistically significant improvement at 6 weeks post BoNT-A and this was maintained across the 12 months.

PEMCI

- Home participation and involvement in home activities significantly improved at 6 weeks and 6 months post-injection, whilst the average frequency of participation in home activities significantly improved at 6 weeks and was maintained throughout the 12 months.
- School participation was only significantly improved (both frequency and involvement in activities) at six months post injection, but was not significantly improved at 6 weeks or 12 months post BoNT-A.
- Community participation neither frequency nor involvement was found to be significantly changed at any time point post BoNT-A injections.

Chapter 8 Hierarchical Multilevel Regression model

The study aimed to evaluate the effect of BoNT-A treatment on outcome throughout the ICF domains. The univariate analysis in the previous chapters provided information about changes in ICF outcomes across the 12 months following BoNT-A treatment, however, these did not take into account the influence of clinical confounders. A multilevel model was therefore considered appropriate to further analyse the data. This accounted for the longitudinal nature of the data with the repeated measurements of each individual defining the level element of the multilevel model.

As this was a pragmatic clinical study with a varied heterogeneous presentation of GMFCS Levels I, II and III, multilevel linear regression modelling was fitted to each outcome in order to calculate the effect of BoNT-A treatment after adjustment for relevant clinical confounders.

The outcome measures used in the multilevel modelling are summarised in Figure 8-1. These were measured on a numerical scale and assessed at 4 different time points: Baseline pre-injection at T0; 6 weeks post-injection at T1; 6 months post-injection at T2; 12 months post injection at T3. Results from the linear multilevel model were interpreted regarding the impact of BoNT-A treatment on the average values of each outcome following adjustment for clinical confounders.

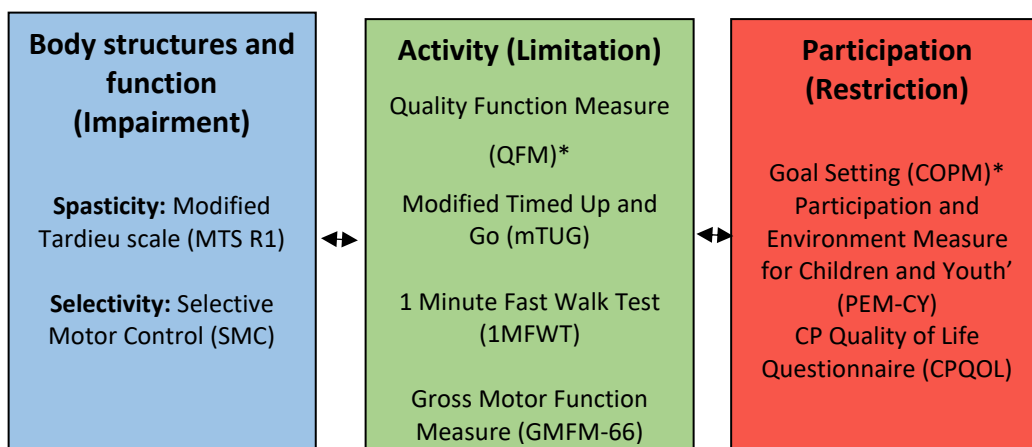


Figure 8-1 Study outcome measures within ICF Domains used for multilevel regression analysis * Primary outcome measures

The confounders considered clinically relevant were;

- GMFCS level
- Age
- Previous injection history
- Unilateral versus bilateral injections
- Injected muscle group (distal, proximal, or multilevel)
- Re-injection within the study

The use of multilevel regression analysis is relatively unique in the field of CP research. The majority of studies evaluating efficacy of BoNT-A treatment for CYPwCP do not adjust for the heterogeneity of the participants studied or attempt to incorporate the complexity of different treatment plans. The aim of this clinically focused research study was to examine the adjusted effects of BoNT-A treatment over a twelve-month period whilst accounting for clinical confounders by using multilevel modelling.

When fitting models, it is possible to increase the probability of significance by adding parameters but doing so may result in overfitting. The Bayesian information criterion (BIC) is a criterion for model selection among a fixed set of models. The BIC solves this problem by introducing a penalty term for the number of parameters in the model. BIC has been widely used for model identification in time series and linear regression (AKAIKE, 1979).

Each model was evaluated against the null model (the model with no confounders) and in all cases, except for PEM-CY participation scores, the fully adjusted model (including all confounders) was found to be a better model as indicated by lower Bayesian Information Criterion (BIC) (See Appendix 14.8.5).

The aim in this study was not to find the best fit from a statistically significant model but to adjust for confounders. The hierarchical multiple regression analysis allowed the effect of BoNT-A injections to be assessed over time throughout the ICF domains after all potential clinical confounders had been accounted for. In

regression with multiple independent variables, the coefficient indicates how much the dependent variable is expected to increase when that independent variable increases by one, holding all the other independent variables constant.

This chapter summarises the results for the multilevel regression and presents the complete regression model for each outcome. The fitted linear multilevel regression model to account for the effect of BoNT-A treatment with time on the sample is presented in the text and tables for each individual outcome. These summarise the details and significance of the confounding variables on the individual ICF outcome in the model.

8.1 Primary outcome measures

8.1.1 QFM

Complete models for all QFM Attributes can be found in the following Table 8-1-Table 8-4) below, all statistically significant results are highlighted in **green** and clinically significant results related to published MDC values in **blue**.

As can be seen from the adjusted coefficients after taking into account the clinical confounders there was a statistically significant improvement in all QFM attribute scores following BoNT-A injections at all post injection assessments 6 weeks, 6 months and 12 months post injection. Although adjusted coefficients were generally lower than those found in univariate analyses, the statistical trends were similar.

The QFM demonstrated the ability to discriminate between GMFCS levels in each attribute, children in GMFCS level III scored lower than children in GMFCS I and II after adjusting for all other confounders, and older children showed significantly higher QFM scores than younger children.

In all QFM attributes apart from Alignment, children with proximal muscle injections scored significantly lower (as shown in the adjusted coefficients) than children who had distal muscles injected, as did children with bilateral injections in comparison to those with unilateral injections.

In order to assess the clinical significance of these statistically significant changes, adjusted coefficients for QFM attributes were subsequently compared to published MDC₈₀ values (Wright et al., 2014a) (Table 6-1). The clinical significance of these changes differed between the individual QFM attributes when compared to the published MDC values.

QFM Alignment scores were found to be both statistically and clinically significantly improved at all post injection time points across the 12 months, whereas QFM Co-ordination, Dissociated Movement, and Weight shift adjusted coefficient scores

showed a clinically significant improvement in comparison to baseline at 6 and 12 months but not at 6 weeks post BoNT-A. Interestingly, improvement in QFM Stability scores approached clinical significance at 6 months but only exceeded minimum detectable change at 12 months post injection.

Each complete QFM attribute model is considered briefly in turn.

QFM Alignment

The average change in adjusted coefficients for QFM Alignment (Table 8-1) exceeded published MDC₈₀ scores (13.5%) at all post injection time points suggesting a clinically significant improvement in average alignment score at 6 weeks post injection which was maintained at 6 and 12 months.

QFM Attribute	Alignment	% Score	P- value	95% Confidence Interval	
		Estimate	P- value	Lower bound	Upper bound
Reference	(Intercept)	63.99	<0.001	54.56	73.45
Baseline T0	T1	15.64	<0.001	12.94	18.33
	T2	14.16	<0.001	11.48	16.81
	T3	16.29	<0.001	13.61	19.03
GMFCS I	GMFCS II	-3.24	0.48	-11.55	5.06
	GMFCS III	-37.96	<0.001	-49.35	-26.55
Younger child (4-8 years)	Older child 9-18 years	11.08	0.02	2.76	19.4
Toxin naive	2nd to 4th injections	1.68	0.7	-6.22	9.56
	5th or more	0.86	0.89	-10.88	12.6
Distal muscles	Proximal Muscles	-4.85	0.42	-15.86	6.16
	Multilevel Muscles	-4.72	0.35	-13.84	4.38
Unilateral distribution	Bilateral distribution	-5.67	0.28	-15.1	3.76
Single injection cycle	Re-injection in study	1.61	0.67	-5.33	8.53

Table 8-1 Complete multilevel regression model for QFM Alignment

QFM Co-ordination

Although co-ordination scores were statistically significantly improved at all time points following BoNT-A, a clinically significant improvement in co-ordination scores was not seen until six months post injection (exceeding the minimal detectable change (MDC₈₀) of 8.7%) and this improvement remained clinically significant at 12 months (Table 8-2).

QFM Attribute	Co-ordination	% Score	P- value	95% Confidence Interval	
				Estimate	Pr(> t)
Reference	(Intercept)	75.97	<0.001	68.02	83.92
Baseline T0	T1	7.74	<0.001	6.02	9.46
	T2	9.69	<0.001	7.99	11.39
	T3	9.66	<0.001	7.95	11.4
GMFCS I	GMFCS II	-5.09	0.19	-12.12	1.94
	GMFCS III	-44.85	<0.001	-54.51	-35.2
Younger child (4-8 years)	Older child 9-18 years	9.48	0.02	2.44	16.51
Toxin naive	2 to 4 injections	2.75	0.46	-3.94	9.42
	5 or more	2.69	0.62	-7.25	12.63
Distal muscles	Proximal Muscles	-11.2	0.03	-20.53	-1.88
	Multilevel Muscles	-0.17	0.97	-7.89	7.54
Unilateral distribution	Bilateral distribution	-10.48	0.02	-18.46	-2.48
Single injection cycle	Re-injection in study	-1.95	0.55	-7.82	3.91

Table 8-2 Complete multilevel regression model for QFM Co-ordination

QFM Dissociated Movement

The results suggested that the average change in adjusted coefficients of QFM Dissociated Movement scores, were statistically significantly improved from baseline at all post injection time points, as shown in Table 8-3 below. The results indicate that this improvement was not clinically significant at 6 weeks post injection as the average score did not exceed the published MDC₈₀ (8.4%). However, by six months the average change scores exceeded the published MDCs suggesting a clinically significant which was maintained at 12 months.

QFM Attribute	Dissociated Movement	% Score	P- value	95% Confidence Interval	
				Estimate	Pr(> t)
Reference	(Intercept)	59.86	<0.001	53.74	66.01
Baseline T0	T1	7.83	<0.001	5.98	9.68
	T2	8.48	<0.001	6.65	10.31
	T3	9.91	<0.001	7.37	11.09
GMFCS I	GMFCS II	-5.79	0.05	-11.18	-0.4
	GMFCS III	-37.18	<0.001	-44.58	-29.79
Younger child (4-8 years)	Older child 9-18 years	12.04	<0.001	6.64	17.44
Toxin naive	2 to 4 injections	2.63	0.35	-2.49	7.74
	5 or more	3.08	0.46	-4.54	10.7
Distal muscles	Proximal Muscles	-9.9	0.01	-17.04	-2.76
	Multilevel Muscles	-1.1	0.74	-7.02	4.81
Unilateral distribution	Bilateral distribution	-8.84	0.01	-14.95	-2.71
Single injection cycle	Re-injection in study	-0.09	0.97	-4.59	4.4

Table 8-3 Complete multilevel regression model for QFM Dissociated Movement

QFM Stability

The average change in adjusted coefficients of QFM Stability scores were statistically significantly improved from baseline at all post injection time points, as shown in Table 8-4 below. However, the adjusted coefficients did not exceed minimal detectable change scores (MDC₈₀-9.9%) at 6 weeks or 6 months post injection, but did reach MDC values at 12 months., suggesting that a clinically significant improvement in stability was only evident 12 months post injection.

QFM Attribute	Stability	% Score	P- value	95% Confidence Interval	
				Estimate	Pr(> t)
Reference	(Intercept)	70.56	<0.001	62.7	78.43
Baseline T0	T1	7.59	<0.001	5.75	9.44
	T2	8.72	<0.001	6.89	10.54
	T3	9.91	<0.001	7.96	11.68
GMFCS I	GMFCS II	-3.84	0.32	-10.79	3.1
	GMFCS III	-45.12	<0.001	-54.66	-35.58
Younger child (4-8 years)	Older child 9-18 years	12.05	<0.001	5.09	19.01
Toxin naive	2 to 4 injections	2.59	0.48	-4.02	9.18
	5 or more	1.81	0.74	-8.02	11.63
Distal muscles	Proximal Muscles	-10.89	0.04	-20.11	-1.67
	Multilevel Muscles	-0.68	0.87	-8.32	6.94
Unilateral distribution	Bilateral distribution	-11.48	0.01	-19.37	-3.58
Single injection cycle	Re-injection in study	-1.26	0.69	-7.06	4.54

Table 8-4 Complete multilevel regression model for QFM Stability

QFM Weight shift

The adjusted coefficients for QFM Weight shift were statistically significantly improved from baseline at all post injection assessments (Table 8-5). However, these adjusted coefficients did not exceed minimal detectable change scores (MDC₈₀- 8.4%) at 6 weeks post injection and reached MDC value at 6 months, only exceeding MDC values at 12 months. This suggested that there may have been a clinically significant improvement in Weight shift by 6 months which further improved at 12 months post injection.

QFM Attribute	Weight shift	% Score Estimate	P- value Pr(> t)	95% Confidence Interval	
				Lower bound	Upper bound
Reference	(Intercept)	62.22	<0.001	55.66	68.78
Baseline T0	T1	7.86	<0.001	6.33	9.39
	T2	8.48	<0.001	6.86	9.89
	T3	9.94	<0.001	8.41	11.5
GMFCS I	GMFCS II	-2.55	0.42	-8.34	3.24
	GMFCS III	-33.35	<0.001	-41.31	-25.4
Younger child (4-8 years)	Older child 9-18 years	10.5	<0.001	4.7	16.3
Toxin naive	2 to 4 injections	4	0.19	-1.5	9.5
	5 or more	3.76	0.41	-4.43	11.95
Distal muscles	Proximal Muscles	-9.33	0.03	-17.02	-1.65
	Multilevel Muscles	-1.69	0.63	-8.05	4.66
Unilateral distribution	Bilateral distribution	-7.74	0.04	-14.32	-1.15
Single injection cycle	Re-injection in study	0.03	0.99	-4.8	4.86

Table 8-5 Complete multilevel regression model for QFM Weight shift

QFM summary of response

The results demonstrated adjusted coefficients for Alignment exceeding published MDCs at all time points, suggesting clinical improvement following BoNT-A. However, an improvement in Alignment scores was not accompanied by clinically significant improvements in other QFM attributes at 6 weeks. Whilst other QFM attributes demonstrated a clinically significant improvement at 6 months, improvement in Stability scores only exceeded MDC values at 12 months.

This suggests that although movement quality was improved for 4 out of 5 attributes following BoNT-A treatment, gains in stability did not reach clinical significance until 12 months post injection.

QFM attributes were shown to be strongly correlated at all time points (6.1.5), questioning the need for separate score analysis. However, correlation reflects an association between the scores rather than agreement between scores. The results shown here suggest that in terms of clinical planning for rehabilitation programmes there may be value in knowing about change scores in specific QFM attributes for the purpose of outcome evaluation and targeted goal setting following treatment.

When compared to the MDC₉₅ values established for the study (Table 6-7), improvement in adjusted QFM scores suggested a significant improvement in all QFM attributes (except QFM Stability) at 6 weeks and for all attribute scores at 6- and 12-months post BoNT-A.

8.1.2 COPM

Complete models for COPM Performance and Satisfaction scores can be found in Table 8-6 and Table 8-7. Statistically significant results have been highlighted in **green** and clinically significant results related to published MCID values in **blue**.

COPM Performance score	COPM-P	Score (1-10)	P- value	95% Confidence Interval	
		Estimate	Pr(> t)	Lower bound	Upper bound
Reference	(Intercept)	3.23	<0.001	2.33	4.13
Baseline T0	T1	2.54	<0.001	2.07	3
	T2	1.75	<0.001	1.28	2.22
	T3	2.49	<0.001	2.02	2.97
GMFCS I	GMFCS II	-0.02	0.95	-0.79	0.74
	GMFCS III	0.24	0.67	-0.81	1.29
Younger child (4-8 years)	Older child 9-18 years	0.85	0.05	0.08	1.62
Toxin naive	2 to 4 injections	-0.43	0.28	-1.16	0.3
	5 or more	0.6	0.31	-0.48	1.69
Distal muscles	Proximal Muscles	-0.16	0.77	-1.18	0.85
	Multilevel Muscles	-0.75	0.11	-1.6	0.09
Unilateral distribution	Bilateral distribution	0.59	0.22	-0.28	1.46
Single injection cycle	Re-injection in study	-0.15	0.67	-0.79	0.49

Table 8-6 Complete multilevel regression model for COPM-Performance

COPM P scores were statistically significantly improved at all time points in comparison to baseline scores. Whilst COPM Performance scores exceeded MCID ≥ 2 at 6 weeks and 12 months, suggesting a meaningful change, these were not clinically significant at T2.

Age appeared to be a weak clinical predictor for improved goal attainment but as this value was less than MCID of 2 this may not represent a clinically relevant difference.

COPM Satisfaction scores suggested a clinically significant improvement in addition to statistical significance at all post injection time points in comparison to baseline scores (Table 8-7).

COPM Satisfaction score		Score (1-10)	P- value	95% Confidence Interval	
				Estimate	Pr(> t)
Reference	(Intercept)	3.1	<0.001	2.06	4.14
Baseline T0	T1	2.78	<0.001	2.22	3.34
	T2	2.03	<0.001	1.47	2.59
	T3	2.79	<0.001	2.22	3.36
GMFCS I	GMFCS II	0.01	0.99	-0.88	0.89
	GMFCS III	0.56	0.4	-0.65	1.77
Younger child (4-8 years)	Older child 9-18 years	0.75	0.13	-0.13	1.64
Toxin naive	2 to 4 injections	-0.86	0.06	-1.7	-0.03
	5 or more	0.09	0.9	-1.16	1.34
Distal muscles	Proximal Muscles	-0.17	0.79	-1.33	1
	Multilevel Muscles	-0.96	0.08	-1.93	0.02
Unilateral distribution	Bilateral distribution	0.78	0.16	-0.22	1.78
Single injection cycle	Re-injection in study	-0.1	0.8	-0.83	0.63

Table 8-7 Complete multilevel regression model for COPM Satisfaction

Unlike the findings from the QFM models there were no significant predictors apart from time in the COPM- S model, suggesting that change in COPM-S scores did not appear to be related to GMFCS level, age or previous injection history within this study.

8.2 Secondary outcome measures

The results for multilevel regression modelling are presented for ICF continuous outcome data.

8.2.1 Body structure and Function

Dynamic Spasticity scores (MTS R1): Gastrocnemius muscle injections

After adjusting for all clinical confounders, dynamic spasticity (R1) was significantly reduced in injected gastrocnemius muscles at 6 weeks and 12 months post injection in comparison to baseline values, but this improvement was not found to be statistically significant at 6 months. The results suggested a clinically significant change occurred at 6 weeks but not at 12 months ($\geq 5^\circ$ SEM (McDowell et al., 2000)). After adjusting for other confounders, the children who required re-injection in the study had on average a greater dynamic catch at baseline (-18.3°) than those children who underwent a single injection cycle in the study.

BSF	Gastrocnemius dynamic catch R1	Degrees °	P- value	95% Confidence Interval	
		Estimate	Pr(> t)	Lower bound	Upper bound
Reference	(Intercept)	-18.13	<0.001	-23.02	-13.22
Baseline T0	T1	5.98	<0.001	3.83	8.14
	T2	1.67	0.14	-0.52	3.84
	T3	3.01	0.01	0.83	5.21
GMFCS I	GMFCS II	0.47	0.84	-3.78	4.73
	GMFCS III	-4.23	0.19	-10.11	1.65
Younger child (4-8 years)	Older child 9-18 years	1.93	0.43	-2.61	6.45
Toxin naive	2nd to 4th injections	2.57	0.21	-1.22	6.34
	5 th or more	6.12	0.1	-0.7	12.91
Distal muscles	Proximal Muscles	0.58	0.79	-3.46	4.62
	Multilevel Muscles	-0.92	0.71	-5.54	3.69
Unilateral distribution	Bilateral distribution	-1.19	0.54	-4.81	2.42
Single injection cycle	Re-injection in study	-18.13	<0.001	-23.02	-13.22

Table 8-8 Complete multilevel regression model for MTS R1 Gastrocnemius muscle

Dynamic Spasticity scores (MTS R1): Hamstring muscle injections

After adjusting for all confounders, dynamic spasticity was reduced in Hamstring muscles at all time points over the 12 months following BoNT-A injections. Whilst the largest reduction in dynamic catch occurred at 6 weeks post injection, the results suggested that there was a clinically significant change at each post injection assessment point (\geq SEM 10° (McDowell et al., 2000)).

BSF	Hamstring dynamic catch R1	Degrees °	P- value	95% Confidence Interval	
		Estimate	Pr(> t)	Lower bound	Upper bound
Reference	(Intercept)	80.7	<0.001	60.22	101.35
Baseline T0	T1	-19.07	<0.001	-23.65	-14.49
	T2	-10.63	<0.001	-15.31	-6
	T3	-10.67	<0.001	-15.49	-6.03
GMFCS I	GMFCS II	20.12	0.01	8.17	32.11
	GMFCS III	24.64	<0.001	12.15	37.13
Younger child (4-8 years)	Older child 9-18 years	10.15	0.05	1.39	18.84
Toxin naive	2nd to 4th injections	3.47	0.42	-3.97	10.91
	5 th or more	-9.8	0.2	-22.95	3.17
Distal muscles	Proximal Muscles	-10.33	0.13	-22.15	1.37
	Multilevel Muscles	-4.25	0.61	-18.79	10.27
Unilateral distribution	Bilateral distribution	-12.77	0.14	-27.75	2.17
Single injection cycle	Re-injection in study	-11.51	0.01	-18.71	-4.33

Table 8-9 Complete multilevel regression model for MTS R1 Hamstring muscle

Age and GMFCS level were significant confounders in the model. Older children had more spasticity with a greater dynamic catch ($\sim 10^\circ$) than younger children. Children in GMFCS II and III had greater dynamic catch in Hamstrings in comparison to children in GMFCS I.

It is of note that children who had re-injection within the study period had lower spasticity scores (less of a dynamic catch) when adjusting for other confounders than those children who only received one injection cycle. This was also highlighted in univariate analysis (Figure 7-5), children who had hamstring re-injection showed

greater reduction in dynamic catch at T1 and T2 but showed greater variability in scores than children who received a single injection during the study. The clinical reasoning around patient selection for re-injection is multifaceted, one explanation could be children with a greater dynamic catch at T2 may not have been eligible for re-injection due to the development of a fixed contracture which would preclude further BoNT-A treatment.

Muscle selectivity- SMC

Although conventionally considered an ordinal scale, SMC scores have also been presented in the literature by the test developers as continuous data with parametric analysis (Boyd et al., 2000). In order to gain further information regarding change in muscle selectivity following BoNT-A, SMC scores were also analysed using multilevel modelling.

After adjusting for confounders, average SMC scores increased significantly at each assessment time point over 12 months following BoNT-A injections (Table 8-10). This suggested an improvement in muscle selectivity following injections, however in the absence of published MCIDs it is difficult to interpret the clinical significance of these change scores.

Significant confounders were GMFCS level, as expected children in GMFCS III scored lower than children in GMFCS I, suggesting more impaired motor selectivity. Children who had proximal muscles injected also had significantly lower SMC scores than those children who had distal muscles injected. Older children showed greater muscle selectivity than younger children when adjusting for all other confounders. Interestingly, children who had bilateral injections had higher SMC scores on average than those with unilateral injections. This could be explained by a predominance of unilateral gastrocnemius injections usually associated with asymmetry due to increased spasticity and can be accompanied by a greater lack of selective motor control in the affected side.

BSF	SMC	Score	P- value	95% Confidence Interval	
				Lower bound	Upper bound
		Estimate	Pr(> t)		
Reference	(Intercept)	2.06	<0.001	1.54	2.58
Baseline T0	T1	0.32	<0.001	0.17	0.46
	T2	0.38	<0.001	0.23	0.52
	T3	0.46	<0.001	0.31	0.61
GMFCS I	GMFCS II	-0.05	0.83	-0.53	0.42
	GMFCS III	-1.54	<0.001	-2.13	-0.95
Younger child (4-8 years)	Older child 9-18 years	0.54	0.03	0.1	0.98
Toxin naive	2nd to 4th injections	-0.05	0.8	-0.44	0.34
	5th or more	0.66	0.06	0.02	1.3
Distal muscles	Proximal Muscles	-0.65	0.03	-1.2	-0.11
	Multilevel Muscles	-0.24	0.37	-0.72	0.25
Unilateral distribution	Bilateral distribution	1.06	<0.001	0.58	1.55
Single injection cycle	Re-injection in study	0.19	0.34	-0.18	0.56

Table 8-10 Complete multilevel regression model for SMC outcome

8.2.2 Activity

Timed up and Go Test (TUG)

After adjusting for all confounders TUG scores although improved from baseline, were not statistically significantly quicker at 6 weeks post injection. By 6 months post injection (T2), TUG scores had further improved, and children were significantly quicker in performing the task, with further improvement seen at 12 months post injection (T3).

A	TUG	seconds		95% Confidence Interval	
		Estimate	P- value	Lower bound	Upper bound
Reference	(Intercept)	9.55	0.01	3.19	15.91
Baseline T0	T1	-1.26	0.14	-2.93	0.41
	T2	-2.04	0.02	-3.69	-0.39
	T3	-2.33	0.01	-4	-0.65
GMFCS I	GMFCS II	-1.28	0.68	-6.88	4.32
	GMFCS III	16.99	<0.001	9.3	24.69
Younger child (4-8 years)	Older child 9-18 years	-0.76	0.81	-6.37	4.85
Toxin naive	2nd to 4th injections	-5.3	0.07	-10.62	0.02
	5 th or more	-0.93	0.83	-8.85	6.99
Distal muscles	Proximal Muscles	4.02	0.33	-3.42	11.44
	Multilevel Muscles	1.31	0.7	-4.84	7.46
Unilateral distribution	Bilateral distribution	1.61	0.65	-4.76	7.98
Single injection cycle	Re-injection in study	-1.72	0.5	-6.4	2.96

Table 8-11 Complete multilevel regression model for TUG outcome

The results suggested TUG scores exceeded published MCIDs at all post injection time points with moderate effect size at T1 (1.2s) and large effect size (1.9s) at T2 and T3 (Hassani et al., 2014). As expected, children in GMFCS level III had significantly slower TUG scores than those children in GMFCS level I but TUG scores were not significantly different between children in GMFCS level I and II.

One Minute Fast Walk Test (1MFWT)

After adjusting for all confounders, the distance walked in the 1MFWT was significantly increased at 6 weeks and 12 months post injection in comparison to baseline scores. Although scores increased at 6 months post injection (T2), this change was not statistically significant. The results suggested that the adjusted coefficients were approximately equal to a clinically significant change at 12 months but not at 6 weeks or 6 months (Hassani et al., 2014).

A	1MFWT	metres	P- value	95% Confidence Interval	
				Estimate	Lower bound
Reference	(Intercept)	68.1	<0.001	60.17	76.03
Baseline T0	T1	3.88	0.04	0.32	7.45
	T2	2.67	0.14	-0.86	6.19
	T3	5.69	<0.001	2.13	9.31
GMFCS I	GMFCS II	-1.29	0.73	-8.14	5.51
	GMFCS III	-31.26	<0.001	-40.64	-21.9
Younger child (4-8 years)	Older child 9-18 years	13.28	<0.001	6.43	20.16
Toxin naive	2nd to 4th injections	8.48	0.02	1.99	14.95
	5 th or more	8.14	0.13	-1.53	17.81
Distal muscles	Proximal Muscles	-10.34	0.04	-19.36	-1.3
	Multilevel Muscles	-0.32	0.94	-7.8	7.17
Unilateral distribution	Bilateral distribution	-5.81	0.18	-13.55	1.94
Single injection cycle	Re-injection in study	-1.66	0.6	-7.35	4.04

Table 8-12 Complete multilevel regression model for 1MFWT outcome

In keeping with other studies, results for 1MFWT were able to discriminate between GMFCS level III and children in GMFCS levels I and II (Hassani et al., 2014, McDowell et al., 2005). However this study confirmed the findings of McDowell et al. (2005) and found no significant difference in distance walked between children in GMFCS levels I and II. Older children walked significantly further than younger children and children who had proximal muscles injected walked less distance than those children who had distal muscles injected.

Previous injection history appeared to be significant, and children who were having their first injection didn't walk as far as those who were having injections for the 2nd 3rd or 4th time.

GMFM-66

After adjusting for all confounders, GMFM-66 scores were improved at all time points over the 12 months following BoNT-A injections.

A	GMFM-66	SCORE %		95% Confidence Interval	
		Estimate	P- value	Lower bound	Upper bound
Reference	(Intercept)	78.51	<0.001	73.97	83.05
Baseline T0	T1	2.38	<0.001	1.49	3.27
	T2	3.46	<0.001	2.58	4.34
	T3	4.56	<0.001	3.67	5.46
GMFCS I	GMFCS II	-2.35	0.29	-6.37	1.67
	GMFCS III	-19.65	<0.001	-25.17	-14.13
Younger child (4-8 years)	Older child 9-18 years	7.95	<0.001	3.93	11.98
Toxin naive	2nd to 4th injections	2.43	0.25	-1.39	6.25
	5 th or more	1.25	0.69	-4.44	6.93
Distal muscles	Proximal Muscles	-5.64	0.06	-10.97	-0.3
	Multilevel Muscles	-0.88	0.72	-5.3	3.53
Unilateral distribution	Bilateral distribution	-5.75	0.03	-10.32	-1.18
Single injection cycle	Re-injection in study	0.26	0.89	-3.09	3.62

Table 8-13 Complete multilevel regression model for GMFM-66 outcome

The results suggested a clinically significant improvement in gross motor function at each post injection assessment point. These changes were in excess of published MCIDs with a moderate effect size at T1 and large effect size at T2 and T3 (Oeffinger et al., 2008, Smits et al., 2013, Wang and Yang, 2006).

Once again GMFCS level was a significant predictor, as expected children in GMFCS I scored significantly higher than children in GMFCS III, however the difference in scores between children in GMFCS level I and II was not significant. Children with

proximal muscles injected also scored lower than those children with distal injections and with a similar magnitude, children with bilateral muscles injected, scored lower in comparison to those children who only had unilateral injections.

8.2.3 Participation

Cerebral Palsy Quality of Life Measure (CPQOL)

The Cerebral Palsy Quality of Life Measure (CPQOL) was used to assess wellbeing across two domains: Participation and physical health (Participation) and Feelings about functioning (Function).

After adjusting for all confounders CPQOL Participation and Function scores were statistically significantly increased at all times post injection in comparison to baseline scores (Table 8-14 and Table 8-15). Previous studies using CPQOL to evaluate change have suggested that change scores $\geq 5\%$ could be clinically significant (Pennington et al., 2020).

The results in this study suggest that improvement could represent a clinically significant change at all time points post injection for change in Participation scores (Table 8-14), but only at 6 weeks and 6 months for change in Function scores (Table 8-15). However, in the absence of MCIDs this is difficult to confirm.

Within this model there did not appear to be any significant predictors of CPQOL scores from any of the clinical confounders.

A	CPQOL Participation	SCORE %	P- value	95% Confidence Interval	
				Estimate	Lower bound
Reference	(Intercept)	57.88	<0.001	48.38	67.41
Baseline T0	T1	7.87	<0.001	4.43	11.26
	T2	8.62	<0.001	5.2	12.03
	T3	7.53	<0.001	4.05	11.04
GMFCS I	GMFCS II	2.89	0.53	-5.39	11.16
	GMFCS III	1.12	0.86	-10.23	12.49
Younger child (4-8 years)	Older child 9-18 years	3.7	0.42	-4.6	11.98
Toxin naive	2nd to 4th injections	-2.12	0.63	-10	5.75
	5 th or more	1.53	0.81	-10.23	13.22
Distal muscles	Proximal Muscles	6.4	0.29	-4.59	17.38
	Multilevel Muscles	-4.23	0.4	-13.35	4.85
Unilateral distribution	Bilateral distribution	-1.86	0.72	-11.26	7.55
Single injection cycle	Re-injection in study	-5.21	0.17	-12.12	1.7

Table 8-14 Complete multilevel regression model for CPQOL Participation outcome

Participation	CPQOL Function	SCORE %	P- value	95% Confidence Interval	
				Estimate	Lower bound
Reference	(Intercept)	66.35	<0.001	58.29	74.44
Baseline T0	T1	6.22	<0.001	3.84	8.61
	T2	5.47	<0.001	3.09	7.86
	T3	4.54	<0.001	2.12	7
GMFCS I	GMFCS II	2.5	0.52	-4.59	9.58
	GMFCS III	0.49	0.93	-9.22	10.23
Younger child (4-8 years)	Older child 9-18 years	3.29	0.40	-3.81	10.37
Toxin naive	2nd to 4th injections	-0.22	0.95	-6.97	6.5
	5 th or more	4.75	0.39	-5.3	14.76
Distal muscles	Proximal Muscles	0.18	0.97	-9.22	9.59
	Multilevel Muscles	-4.71	0.27	-12.5	3.06
Unilateral distribution	Bilateral distribution	1.88	0.67	-6.18	9.93
Single injection cycle	Re-injection in study	-3.63	0.27	-9.55	2.28

Table 8-15 Complete multilevel regression model for CPQOL Function outcome

Participation Environment Measure (PEM-CY)

The Participation Environment Measure Child and Youth (PEM-CY) was used to assess two components of Participation: Average frequency of activities (Frequency) and Average involvement in Activities (Involvement) in three settings, home, school and community.

Home

After adjusting for all confounders, PEM-CY Home Participation scores both for *frequency* of participation activities (Table 8-16) and *involvement* in home participation activities (Table 8-17) were significantly increased at all times post injection in comparison to baseline scores. However, in the light of the small change values and absence of MCIDs the clinical significance of the adjusted coefficients is difficult to interpret.

Home Participation	Frequency of participation	SCORE (0-7)	P- value	95% Confidence Interval	
				Lower bound	Upper bound
Reference	(Intercept)	5.81	<0.001	5.25	6.36
Baseline T0	T1	0.27	<0.001	0.14	0.41
	T2	0.3	<0.001	0.16	0.44
	T3	0.24	<0.001	0.1	0.39
GMFCS I	GMFCS II	-0.1	0.7	-0.59	0.39
	GMFCS III	-0.15	0.68	-0.83	0.52
Younger child (4-8 years)	Older child 9-18 years	-0.14	0.6	-0.63	0.35
Toxin naive	2nd to 4th injections	-0.31	0.22	-0.78	0.15
	5 th or more	-0.29	0.45	-0.98	0.4
Distal muscles	Proximal Muscles	0.22	0.55	-0.43	0.88
	Multilevel Muscles	0.05	0.87	-0.49	0.59
Unilateral distribution	Bilateral distribution	-0.31	0.31	-0.87	0.25
Single injection cycle	Re-injection in study	0.05	0.83	-0.36	0.45

Table 8-16 Complete multilevel regression model for PEM-CY Home Frequency Participation outcome

Home Participation	Involvement in participation	SCORE (0-5)	P- value	95% Confidence Interval	
				Estimate	Lower bound
Reference	(Intercept)	3.92	<0.001	3.61	4.22
Baseline T0	T1	0.23	<0.001	0.09	0.37
	T2	0.26	<0.001	0.12	0.4
	T3	0.24	<0.001	0.1	0.39
GMFCS I	GMFCS II	0.09	0.51	-0.16	0.35
	GMFCS III	0.07	0.71	-0.28	0.43
Younger child (4-8 years)	Older child 9-18 years	0.28	0.05	0.02	0.54
Toxin naive	2nd to 4th injections	-0.23	0.09	-0.48	0.02
	5 th or more	-0.29	0.15	-0.66	0.07
Distal muscles	Proximal Muscles	0.03	0.89	-0.32	0.38
	Multilevel Muscles	0.04	0.81	-0.25	0.32
Unilateral distribution	Bilateral distribution	-0.09	0.57	-0.39	0.2
Single injection cycle	Re-injection in study	0.11	0.35	-0.1	0.33

Table 8-17 Complete multilevel regression model for PEM-CY Home Involvement Participation outcome

Involvement in participation in home activities was improved at 6 weeks post injection and this was maintained at 6 and 12 months. Younger children appeared to participate more than older children in home activities. However, once again, in the light of the small change values and absence of MCIDs, the clinical significance of the adjusted coefficients is difficult to interpret.

School

After adjusting for all confounders PEM-CY Participation scores for school *involvement* (Table 8-18) were significantly increased at all times post injection in comparison to baseline scores. Involvement in school activities improved at 6 weeks and this improvement was maintained at 6- and 12-months post injection. However, *frequency* of school participation scores (Table 8-19) were only significantly improved at 6 months post injection in comparison to baseline frequency of school participation scores. Once again, this improvement in scores could suggest clinical significance for improved school participation and

involvement scores, however, in the absence of MCIDs the clinical significance of the adjusted coefficients is difficult to interpret.

School Participation	Frequency of participation	SCORE (0-7)	95% Confidence Interval		
			Estimate	P- value	Lower bound
Reference	(Intercept)	4.01	<0.001	3.37	4.65
Baseline T0	T1	0.17	0.21	-0.09	0.43
	T2	0.44	<0.001	0.18	0.69
	T3	0.24	0.68	-0.02	0.51
GMFCS I	GMFCS II	-0.13	0.05	-0.7	0.45
	GMFCS III	-0.88	0.57	-1.68	-0.09
Younger child	Older child 9-18 years	0.18	0.92	-0.38	0.73
Toxin naive	2nd to 4th injections	-0.03	0.96	-0.55	0.5
	5 th or more	0.02	0.52	-0.76	0.81
Distal muscles	Proximal Muscles	0.26	0.37	-0.47	1.01
	Multilevel Muscles	0.32	0.87	-0.31	0.95
Unilateral distribution	Bilateral distribution	0.06	0.21	-0.58	0.7
Single injection cycle	Re-injection in study	-0.33	0.68	-0.8	0.14

Table 8-18 Complete multilevel regression model for PEM-CY School Frequency of Participation outcome

School Participation	Involvement in participation	SCORE (0-5)	95% Confidence Interval		
			Estimate	P- value	Lower bound
Reference	(Intercept)	3.95	<0.001	3.51	4.4
Baseline T0	T1	0.21	0.02	0.03	0.38
	T2	0.17	0.05	0	0.35
	T3	0.22	0.02	0.04	0.4
GMFCS I	GMFCS II	0.2	0.37	-0.2	0.6
	GMFCS III	0.41	0.18	-0.15	0.97
Younger child	Older child 9-18 years	0.35	0.1	-0.03	0.74
Toxin naive	2nd to 4th injections	0.02	0.93	-0.35	0.39
	5 th or more	-0.09	0.75	-0.64	0.45
Distal muscles	Proximal Muscles	-0.02	0.94	-0.53	0.5
	Multilevel Muscles	-0.19	0.45	-0.62	0.26
Unilateral distribution	Bilateral distribution	-0.34	0.17	-0.79	0.1
Single injection cycle	Re-injection in study	-0.24	0.18	-0.57	0.08

Table 8-19 Complete multilevel regression model for PEM-CY School Involvement in Participation outcome

Community

After adjusting for all confounders PEM-CY participation scores for *frequency* of community activities were significantly increased at all times post injection in comparison to baseline scores (Table 8-20). However, there was no significant improvement in *involvement* in community activities at any time point post injection (Table 8-21).

Community Participation	Frequency of participation	SCORE (0-7)	P- value	95% Confidence Interval	
				Estimate	Lower bound
Reference	(Intercept)	3.23	<0.001	3.37	4.65
Baseline T0	T1	0.3	<0.001	-0.09	0.43
	T2	0.22	0.03	0.18	0.69
	T3	0.3	<0.001	-0.02	0.51
GMFCS I	GMFCS II	-0.6	0.03	-0.7	0.45
	GMFCS III	-0.9	0.02	-1.68	-0.09
Younger child (4-8 years)	Older child 9-18 years	-0.18	0.51	-0.38	0.73
Toxin naive	2nd to 4th injections	-0.29	0.27	-0.55	0.5
	5 th or more	-0.23	0.55	-0.76	0.81
Distal muscles	Proximal Muscles	0.26	0.48	-0.47	1.01
	Multilevel Muscles	0.15	0.62	-0.31	0.95
Unilateral distribution	Bilateral distribution	0.1	0.76	-0.58	0.7
Single injection cycle	Re-injection in study	-0.24	0.31	-0.8	0.14

Table 8-20 Complete multilevel regression model for PEM-CY Community Frequency of Participation outcome

The results suggested that children in GMFCS Level I participated more often in community activities than children in GMFCS Level II and III. However, *involvement* in community participation activities was not significantly improved at any time point post injection in comparison to baseline scores (Table 8-20). Whilst the frequency of Community participation activities improved at 6 weeks and this improvement was maintained at 6 and 12 months, once again in the absence of MCIDs the clinical significance of this magnitude of change is hard to interpret.

Community Participation	Involvement in participation	SCORE (0-5)		95% Confidence Interval	
				Estimate	P- value
Reference	(Intercept)	4.39	<0.001	4.01	4.76
Baseline T0	T1	0.12	0.13	-0.03	0.28
	T2	-0.07	0.37	-0.23	0.08
	T3	0.15	0.06	-0.01	0.31
GMFCS I	GMFCS II	-0.05	0.76	-0.38	0.27
	GMFCS III	0.24	0.33	-0.21	0.69
Younger child (4-8 years)	Older child 9-18 years	0.05	0.76	-0.27	0.38
Toxin naive	2nd to 4th injections	-0.16	0.34	-0.47	0.15
	5 th or more	-0.34	0.18	-0.8	0.12
Distal muscles	Proximal Muscles	0.18	0.46	-0.26	0.61
	Multilevel Muscles	-0.06	0.75	-0.42	0.29
Unilateral distribution	Bilateral distribution	-0.4	0.05	-0.77	-0.03
Single injection cycle	Re-injection in study	-0.18	0.24	-0.45	0.09

Table 8-21 Complete multilevel regression model for PEM-CY Community Involvement in Participation outcome

SUMMARY

The multilevel regression analysis results for primary and secondary outcome measures are summarised in Table 8-22. These are categorised into short term (T1), medium term (T2) and long term (T3) change. These results illustrate both the statistical and clinically significant change in comparison to baseline over a 12-month period following BoNT-A treatment and are highlighted in terms of significant change (green) and non-significant change (red) and unknown clinical significance due to a lack of published MCIDs (yellow).

Multilevel Modelling		Statistical significance			Clinical significance					
		Short term	Medium term	Long term	Short term	Medium term	Long term			
	QFM Alignment	p<.001			☑	☑	☑			
QFM	QFM Coordination				☒	☑	☑			
	QFM Dissociated movement				☒	☑	☑			
	QFM Stability				☒	☒	☑			
	QFM Weight shift				☒	☑	☑			
COPM	COPM-Performance	<.001			☑	☒	☑			
	COPM-Satisfaction	<.001			☑	☑	☑			
	SMC	p<.001								
BSF	MTS R1 Hamstrings	p<.001			☑	☑	☑			
	MTS R1 Gastrocnemius	p<.001	☒	p=.01	☑	☒	☒			
ACTIVITY	1MFWT	p=.04	☒	p<.001	☒	☒	☑			
	TUG	☒	p=.02	p=.01	☒	☑	☑			
	GMFM66	p<.001			☑	☑	☑			
PARTICIPATION	CPQOL Function	p<.001								
	CPQOL Participation	p<.001								
	PEM-CY Home average frequency	p<.001								
	PEM-CY Home average involvement	p<.001								
	PEM-CY School average frequency	☒	p<.001	☒						
	PEM-CY School average involvement	p=.02	p=.05	p=.02						
	PEM-CY Community average frequency	p<.001	p=.03	p<.001						
	PEM-CY Community average involvement	☒	☒	☒						
Key:		Significant ☑			Not significant ☒			No published MCID/MDC		

Table 8-22 Summary of the results from the Hierarchical Multilevel Regression Models

Short term:6 weeks Medium term:6 months Long term:12 months

Chapter 9 Phase I Discussion

This study aimed to evaluate change in ambulant CYPwCP within the Body structure and function, Activity and Participation domains of the ICF over 12 months following lower limb BoNT-A treatment. The use of multilevel modelling permitted the analysis of treatment outcome whilst accounting for the heterogeneity of the participants. Adjusting for confounders allowed the analysis of change in all GMFCS levels including the different CP distributions (unilateral and bilateral) and acknowledged the complexity of treatment patterns which involved different muscle groups and varied previous injection history.

The data suggested that there was a significant improvement in movement quality, gross motor function and goal attainment across the 12 months following BoNT-A treatment. The changes were combined with improved muscle selectivity together with a reduction in dynamic muscle spasticity, which varied from short term in the gastrocnemius muscles and more long term in hamstring muscles. The results highlighted a significant increase in children's wellbeing regarding feelings about functioning and participation and physical health. The analysis also identified a significant improvement in the average frequency of children's participation in home and community activities following BoNT-A, however there was less evidence to suggest that children had a significant change in involvement in community participation activities.

In this chapter the results from the study are analysed in terms of change following BoNT-A treatment within the different domains of the ICF. Comparing the findings from this study to the existing literature assists in understanding the relevance of these findings, together with considering their implications for clinical practice.

9.1 Body function and structure (BSF)

9.1.1 BSF Tone reduction

Within the BSF domain the results in this study demonstrated a significant reduction in dynamic muscle tone (spasticity) following BoNT-A treatment. The magnitude of change was in keeping with other BoNT-A work (Delgado et al., 2016b, Kelly et al., 2019, Löwing et al., 2017, Williams et al., 2013a, Wright et al., 2008, Yap et al., 2010).

A reduction in spasticity was detected in both gastrocnemius and hamstring muscles at six weeks by both the Modified Tardieu Scale (R1) (MTS) and Modified Ashworth Scale (MAS). The significant change from baseline scores suggested a clinically significant improvement in spasticity following treatment. This improvement in spasticity was also reflected in the more global 'technical response' score used in the study, which found that 75% of participants had a significant reduction in dynamic muscle tone in comparison to baseline scores at 6 weeks following BoNT-A.

It is well recognised that the measurement of spasticity in CP remains a challenge, and as a result there are a limited number of clinical scales available to quantify altered tone in CYPwCP. However, despite the long term recognition of MTS to be a more sensitive tool to evaluate the presence of spasticity in the paediatric cerebral palsy population than the MAS (Alhusaini et al., 2010, Fleuren et al., 2010, Love et al., 2010b, Multani et al., 2019a, Mutlu et al., 2008, Strobl et al., 2015), the majority of research within the paediatric literature still reports change in spasticity in terms of MAS following BoNT-A treatment (Blumetti et al., 2019).

The continued presence of MAS within the literature encourages others to continue with its use in order to compare outcomes within the published literature. Therefore, MAS was also used in this study in addition to MTS to evaluate change in spasticity from baseline in gastrocnemius and hamstring muscles in order to compare the results from this study with published literature.

However, the amount of agreement between the different measures of spasticity can in some cases be seen to vary. In this study the measures of dynamic spasticity (MTS and MAS) appeared to mirror each other and supported a short term clinically significant change in tone within this study at six weeks. Kelly et al. (2019), also reported a short term improvement in spasticity as measured by both MTS and MAS scores at 8 weeks post injection. In contrast, Delgado et al. (2016b) found significant short-term improvement in MAS scores in favour of BoNT-A, however the reduction in spasticity was not reflected in a significant change in MTS scores post injection. The use of different scales to measure spasticity can make comparisons both between and within studies difficult.

In this study, longer term changes in dynamic muscle tone (MTS) at six and twelve months following BoNT-A, differed between the two main muscle groups injected, gastrocnemius and hamstrings. The data suggested that a clinically significant reduction in dynamic gastrocnemius spasticity only occurred at six weeks post injection whereas dynamic hamstring spasticity improved at six weeks and although reduced in magnitude, remained clinically significant at both six and twelve months post injection.

The disparity in response between different muscle groups is in agreement with other work in the field. Wright et al. (2008) reported the opposite in their study, with a more long-term response shown in gastrocnemius muscle than hamstring muscles. Within pragmatic studies, a variability in response is to be expected when there is more than one muscle group injected. It has been suggested that to capture the complex change occurring when multiple muscle groups are injected more global measures (such as 'technical response', as used in this study) should be used to assist in the evaluation of change in tone post BoNT-A treatment (Heinen et al., 2021).

Whilst the clinical reduction in spasticity has been widely reported to last between three and six months (Franki et al., 2020, Heinen et al., 2010, Mugglestone et al., 2012), this study found that a technical response in the muscle (representing a

clinically significant reduction in dynamic spasticity) was sustained in 51.7 % of all children in the study at six months (following a single injection cycle) and in 53.4% at 12 months (45.2% of those with a single injection and 54.8% of those who had re-injection). This finding is in keeping with other studies in which reduction in spasticity has been described up to 12 months (Delgado et al., 2017b) and 22 months (Löwing et al., 2017) post injection.

These results may have implications for clinical practice and contribute to the discussion regarding the optimisation of re-injection intervals. Although re-injection was associated with reduced dynamic tone (technical response), re-injection status was not found to be associated with any significant difference in activity outcomes for the re-injection group in comparison to the group of children who received a single injection cycle.

This is in keeping with the work of Kanovsky et al. (2009), who found no significant difference in activity outcomes between groups who were injected yearly and more frequently (four months) into the gastrocnemius muscle. The same finding was later confirmed in a study by Hastings-Ison et al. (2016), who also suggested that more frequent re-injection (every four months) may have a detrimental effect by promoting crouch gait in children with bilateral involvement.

It has been suggested that simply maintaining activity and gross motor performance, in the absence of deterioration, could indicate a successful outcome of an intervention such as BoNT-A when one considers the natural progression towards a deterioration in motor abilities in CP (Bell et al., 2002, Rose et al., 2010). In this study whilst there was no significant difference in outcomes between children relative to the number of injection episodes in 12 months, it would appear that the children in the re-injected group required a repeat injection cycle to maintain the same level of activity as those who required only a single injection cycle.

Considering which children may benefit from re-injection is highly relevant for clinical practice. As shown in the regression analysis there were no significant

differences between the two groups (single versus repeat injection) in terms of activity measures at any assessment time point. This was particularly pertinent at six months post injection, when retention of BoNT-A effects was assessed and children evaluated as regards to their need for further BoNT-A treatment. The absence of a significant difference in impairment and activity outcomes between the two groups at six months suggest that decision making regarding the selection of children for retreatment (as for many interventions in CP) is complex and multifactorial. Factors are multidimensional and can include, amongst others, the magnitude of change seen immediately after injections and parental satisfaction with a change in activity and participation. The potential reasons that children are considered for retreatment will be explored further later in the discussion.

9.1.2 BSF Pain

The results showed that pain was reported in 47.4% of the children during the twelve months of this study. This incidence of pain is in keeping with the work of Chaléat-Valayer et al. (2011) who identified pain in 42% of the 228 CYPwCP in their French national study regarding BoNT-A use, and more recently, Eriksson et al. (2020) who reported a pain prevalence of 44% in their large cohort of 3545 CYPwCP in Sweden. However, the latter prevalence was significantly lower than the 60-70% reported in other European studies (Fairhurst et al., 2019, Parkinson et al., 2010). Although both of these studies did include older CYPwCP than the children in this study and Fairhurst et al. (2019) involved CYP in GMFCS levels IV and V, both of which have been associated with higher incidences of pain (McKinnon et al., 2019). Nevertheless, pain is a common experience for many CYPwCP and is often associated with reduced motor activity in ambulant children.

Self-reporting is a criterion standard when assessing pain, however due to the young age of children in this study, parents were asked to score the two pain scores in consultation where possible with their child. Previous work has demonstrated that parent and self-reported pain can be significantly correlated (Spearman rank correlation coefficient 0.45, $p < .001$), although the authors observed that parents

tended to underestimate pain when the child's self-reported pain was frequent and severe (Parkinson et al., 2010).

Average baseline pain scores were low within this study when rated using the modified Faces Pain Scale (2.3 out of 10 \pm 2.4), however, the impact of pain on quality of life evaluated by CPQOL Pain domain was relatively high at 41.2% (\pm 15.5). The CPQOL findings were higher than baseline scores of a similar cohort of children undergoing SDR surgery (36.4%, \pm 18.7)(Summers et al., 2019). This is perhaps not surprising as one of the frequently cited drivers for treatment with BoNT-A in ambulant CYPwCP is to relieve pain following participation activities, with pain reduction frequently chosen as a treatment goal (Elkhatat et al., 2017, McKinnon et al., 2019, Michelsen et al., 2018, Ostojic et al., 2019, Preston et al., 2011).

In our study we found a significant reduction in both pain scores ($p < .001$) at six weeks and six months post injection but although at 12 months pain scores were still improved from baseline these were no longer significant. The improvement in pain reported in this study is in keeping with the work of others including Misra et al.(2010), who also reported significant improvement in baseline pain scores for ambulant CYPwCP ($p < .001$) measured using a visual analogue scale at three months post injection following BoNT-A injections. More recently Caglar et al.(2018) demonstrated significantly reduced reported pain at 4 weeks post injection with improvement maintained at 3 months. Chaléat-Valayer et al. (2011) found that the 119 CYPwCP in their study who had therapeutic goals related to pain reduction following BoNT-A reported an 80% reduction in pain scores at 12 months follow up.

The results from this Toxin Study and others suggest that BoNT-A treatment may be beneficial for reducing pain in ambulant CYPwCP. Although traditionally pain reduction was thought to be mediated by reduction in spasticity and resultant muscle relaxation, there is some evidence that more long-term pain relief following BoNT-A use may be due to other mechanisms. The anti-nociceptive effects of BoNT-A are currently being studied in both animal models and patients with neuropathic pain to explore this association further (Park and Park, 2017).

9.2 Activity and QFM

Research to date has evaluated change in gross motor function following BoNT-A using the GMFM, a gold standard outcome measure to evaluate gross motor *capacity*. This study is the first to report objective findings of change in movement quality (QoM) evaluating gross motor *performance* following BoNT-A injections using the QFM. The QFM was specifically introduced for this study in order to enhance the evaluation of change both in gross motor function and gross motor performance.

There was a significant improvement in GMFM-66 scores at all post injection time points from baseline over 12 months which was associated with significant improvement in QoM. The average changes in GMFM-66 scores in this study exceeded published MCIDs and represented a large effect size at all assessment points throughout the 12 months of the study (Oeffinger et al., 2008). This is in keeping with other published work following BoNT-A, when motor performance continued to improve throughout the study even though dynamic spasticity returned (Bjornson et al., 2007, Caglar Okur et al., 2018, Wright et al., 2008). The results from this study suggest that BoNT-A injections are associated with short-term improvement in dynamic tone but more significantly may also be associated with a longer-term improvement in activity as measured by the gold standard measure of motor function GMFM.

This research represents the largest reported study to date using the QFM to evaluate movement quality in ambulant CYPwCP, involving the analysis of 239 QFM tests over a twelve-month period. A statistically significant improvement in movement quality in all QFM attributes was found at all time points following treatment. These results, demonstrating a change in movement quality following BoNT-A, are novel in the field. After comparing these results to published MDC values, this study found a difference in the timing of clinically significant response between the QFM attributes which could be useful in explaining changes in impairment and activity outcomes following BoNT-A intervention.

The statistically significant improvement in Alignment scores were found to represent a clinically significant change at six weeks, six months and twelve months post injection when compared to published values (Tustin et al., 2016, Wright et al., 2014a). This may be an expected benefit of BoNT-A, as one of the frequent drivers for treatment and purpose of reducing hypertonia is to promote symmetry by improved alignment. However, improved Co-ordination, Dissociated Movement and Weight Shift scores, although statistically significant at all time points, did not exceed the test developers MDC values at six weeks post BoNT-A, taking longer to show clinically significant improvement, which was apparent by six months and maintained at twelve months. Stability scores, although statistically significantly improved at all time points, only showed a clinically significant improvement at 12 months. This suggests that despite changes in other quality attributes, a significant improvement in CYPwCP's stability following BoNT-A may take longer to develop. The difference in timing of improvement in the different QFM attributes may have clinical implications for targeted training post BoNT-A to optimise rehabilitation.

A delay in achieving a clinically significant improvement in co-ordination, dissociated movement, weight shift and particularly stability is perhaps to be expected following BoNT-A when a weakening effect in the injected muscle is to be expected. This difference in timing regarding clinically significant change was also reflected in activity scores, particularly with the Timed up and Go test, which was only significantly improved six months after injection. One explanation for this could be that any changes that occur in tone and alignment following BoNT-A treatment require time for the influence to take effect, suggesting that a child needs the opportunity to adapt to an altered movement pattern. This would support the argument for less frequent injections and longer periods of rehabilitation following treatment, in order for children to be given time to utilise the effects of reduced tone in the muscle.

In reality this is often observed in clinical practice and additionally highlighted in the data from Phase II (Chapter 11). Children talked about the weakening effect of BoNT-A on the injected muscle and the presence of increased trips and falls and

sometimes a worsening of motor performance in the first six weeks following treatment. *“It’s good, but also bad ... because, like, sometimes when I have it, I fall over after I have it”*. A delay in observing improved stability, was also associated with a delay in improved walking capacity as measured by 1MFWT which also only showed clinically significant improvement at twelve months.

This suggestion of a difference in the timing of response has important implications for clinical practice, as some activity outcomes may not have taken effect and children may not have had the chance to reach their full potential following treatment at the first post injection assessment. This may result in suboptimal selection of further treatment plans including overprescribing of BoNT-A or discontinuing further treatment if injections are perceived to have not worked. It is advised that more than one assessment should be carried out following the immediate post injection time point (4-6 weeks) to accurately assess the efficacy of BoNT-A treatment, especially if excessive repeat injections are to be avoided (NICE, 2012). The results from this study would support that approach.

Although the change in 1MFWT scores from baseline reached statistical significance at six weeks and twelve months, this only represented a clinically significant improvement in gait scores at twelve months (moderate effect size), when compared to published MCIDs (Hassani et al., 2014). The results in this study therefore did not appear to demonstrate significant clinical improvement in gait capacity in the first six months following treatment. These findings are in contrast to Delgado et al. (2016b) and others who reported significant improvement in gait up to six months post injection, using gait rating scales and spatiotemporal parameters (Boyd et al., 2000, Ibrahim et al., 2007, Wright et al., 2008, Xu et al., 2006). However, as the results of these other studies were not related to MCIDs, it is difficult to interpret the clinical significance of these gait changes beyond statistical significance.

A number of other researchers in the field also failed to observe significant improvement in gait outcomes following BoNT-A treatment. Thomas et al. (2016)

found no significant improvement in 1MFWT scores following BoNT-A at any point during their six-month study. Kelly et al. (2019), despite reporting significant improvement in motor function, found no significant improvement in spatiotemporal parameters of gait. Similarly, the RCT by Tedroff et al. (2010), found a significant reduction in tone following treatment but this was not associated with any improvement in three-dimensional gait analysis in favour of BoNT-A. These results support the findings of a recent Cochrane review which found limited evidence that BoNT-A is effective in improving gait in CYPwCP (Blumetti et al., 2019). However, some authors have questioned the usefulness of clinic-based walking tests to evaluate true walking performance, claiming that they may be more a measure of walking capacity rather than a reflection of a child's capability or performance (Reedman et al., 2019).

9.3 Goal attainment following BoNT-A

Within paediatric rehabilitation a family centred approach to intervention is now widely accepted. In the last decade there has been a move to embrace this improved approach to service delivery with a focus on the needs of children and their families. It has been recognised that studies regarding the efficacy of BoNT-A use should include the impact of treatment on a child's function and assess meaningful goals in the context of a child's everyday life (NICE, 2012, Sutherland et al., 2022, Tilton et al., 2017, Valentine et al., 2021).

This study used COPM to identify performance issues and individual goals were selected through discussion between children, families and the clinical team to ensure that they were realistic, achievable and meaningful for each child within this study. This is in keeping with the work of Löwing et al. (2017) and Schasfoort et al. (2018) who also allowed children and families to freely choose their goals for BoNT-A treatment. This is in contrast to several earlier studies where the clinicians identified the goals for treatment (Paolicelli et al., 2001, Satila et al., 2008, Weigl et al., 2007), or gave families a predefined list of goals to choose from (Tilton et al., 2017). This detail regarding who sets the goals may be significant, as it has been suggested that children and families are usually more motivated to work towards

goals that they perceive to be important (Kang et al., 2020, Verkerk et al., 2021). It has also been proposed that family-centred therapy including involvement in decision making and collaborative goal setting improves family's satisfaction with rehabilitation interventions (Law et al., 2003, Ostensjø et al., 2008).

Whilst subjective outcomes may be considered susceptible to some forms of bias, goal-based measures are highly appropriate as primary outcome measures for interventions that aim to improve activity and participation (Palisano et al., 2012). The COPM has been used as a primary outcome in several paediatric rehabilitation trials as it has been said to reflect exactly what children, families, and clinicians hope to gain from an intervention (Anaby et al., 2018, Darrah et al., 2011, Imms et al., 2016, Law et al., 2015, Sakzewski et al., 2011).

This study found a significant improvement in both COPM Goal Performance and Satisfaction baseline scores following BoNT-A treatment at 6 weeks post injection and this improvement was maintained throughout the 12 months of the study. The change in COPM appeared to be independent of any clinical confounders and unlike many of the other activity and impairment outcomes there were no significant differences observed between GMFCS levels.

The significant improvement in goal attainment found in this study following BoNT-A treatment was in keeping with the work of a number of researchers in the field using both COPM and Goal Attainment Scaling (GAS). Thomas et al. (2016) also found significant improvement from baseline COPM scores at 10 weeks post injection which were maintained at six months following lower limb BoNT-A injections. The magnitude of change reported at 10 weeks post treatment (2.3-2.9) was in keeping with the results in this study. Short term improvement in goal attainment (up to 12 weeks post injection), was reported in several studies using Goal Attainment Scaling (GAS) (Delgado et al., 2017a, Delgado et al., 2016b, Löwing et al., 2017, Williams et al., 2013a). Improvement was maintained for up to six months (Williams et al., 2013a), 12 months (Delgado et al., 2017b) and 24 months (Löwing et al., 2017).

Bjornson et al. (2007), also found a significant improvement in COPM Performance scores in favour of BoNT-A treatment at 12 weeks post injection, however in their study this was no longer significant at 6 months. Although statistically significant at 12 weeks, the mean change in COPM did not exceed the recommended MCID ≥ 2 points change score and therefore may not have been clinically significant. They also found that COPM Satisfaction scores were not significant at any time point within their study. The authors suggested that despite a significant change in functional outcomes for CYPwCP, the extent of change following treatment, or families' perception of improved function, was not recognised as a meaningful enough improvement in participation to affect parents' satisfaction scores. This failure to demonstrate a match between the measured effect and the perceived benefit of treatment and burden of multiple repeat injections has been recognized as another potential reason why parents may discontinue BoNT-A treatment (Linder-Lucht et al., 2006, Weigl et al., 2007).

In contrast to Bjornson et al. (2007), both COPM Performance and Satisfaction scores were significantly improved from baseline at each assessment time point within this study. When this was related to MCIDs the change was found to be clinically significant exceeding the MCID of ≥ 2 at six weeks and twelve months for performance scores but although statistically significant, these did not appear to be clinically significant at six months (1.8 point change). Within this study Satisfaction scores were clinically significant and consistently rated slightly higher (0.5 points) than Performance scores at all post injection time points over the 12 months. This is in keeping with the work of others including Persson et al. (2004) and Eyssen et al. (2011), who found that the improvement in satisfaction appeared to be greater than the actual change in performance. This may be related to parental expectations and their perception of improved function. As highlighted in Chapter 11, data from Phase II of the study suggested that parents' expectations were realistic in anticipating small changes following BoNT-A treatment. They discussed this in the context of expectations of outcome following BoNT-A treatment and compared this to the greater expectations they would expect following surgical intervention (such as orthopaedics and neurosurgery).

9.3.1 Goal Type

This is one of the few studies to have categorised the individual treatment goals selected by families for BoNT-A treatment into the different ICF domains. Although several researchers have documented the goals set by families for BoNT-A treatment (Fagard et al., 2012, Tilton et al., 2017, Tse et al., 2014, Williams et al., 2014), these did not appear to be related to any classification systems. This can make comparison of goal selection difficult between the studies and make results challenging to interpret.

In this study 57.4 % of the goals set were classified within the ICF domain of Activity and Participation, 37.3% of goals related to body structure and function and only 5.3% were environmental goals (all to do with improved splint tolerance). This was in keeping with the work of McMorran et al. (2016) who used GAS in order to compare outcomes between CYPwCP who had orthopaedic surgery and those who had conservative management including BoNT-A. They found a similar breakdown in goal selection for the children in their non-surgical group, 55.6% of goals were in the Activity and Participation domain, 33.4% were body structures and function and 6.9% were goals related to environmental factors. Both studies confirm that the priorities of children and families when setting goals for interventions are usually focused on improving functional activity and participation.

These findings of goal distribution are in contrast to a retrospective case note review by Preston et al. (2011), who also classified goals into ICF domains. They collected data regarding goal setting for 239 CYPwCP receiving upper and lower limb BoNT-A treatment over a 15-year period. They found that the majority of the goals selected (68.3%), were related to the body structure and function domain, with only 25.7% in the activity and participation domains. The difference in their results could be due to the inclusion of data from children in all GMFCS levels. However, perhaps more relevant is the timing of the study, which included case notes prior to the introduction of the ICF when perhaps more emphasis was placed on the traditional impairment model of targeting body structure and function in

isolation. However, closer inspection with a participation focused lens might suggest that many of the walking goals Preston et al. (2011) classified within the body structure and function domain were in fact related to activity rather than appearance of gait. Within their study, although 55% of goals selected were related to gait, 21% could be classified within the body structure and function domain and the remaining 34% could be classified within the activity and participation domain.

More recently Wong et al. (2022) also described goals for BoNT-A use in terms of the ICF, in a study evaluating 25 children from GMFCS Levels I-V. Twenty nine goals were identified but in contrast to the goals set within this 'Toxin Study', only five of the goals related to a change in activity and participation, the remaining 24 goals related to change in body structure and function domain. However, the high percentage of children in GMFCS Levels IV and V (46.2%) almost certainly accounts for the predominance of body structure and function goals, particularly as 79.2% of these goals were related to sleep function and pain reduction. The authors did not differentiate between the goal setting of ambulant and non ambulant children.

9.3.2 Individual goal scores

Within this study the traditional method of scoring average goal attainment with COPM was used (Law et al., 2019) and the results suggested a significant improvement from baseline, discussed above in the context of the existing literature. However additionally, the 169 individual COPM goals were also categorised within the ICF domains and analysed in order to identify any difference in response between the different domains.

This allowed for individual analysis of all goals set and mirrors pragmatic clinical practice, where change in each individual goal set is evaluated during a child's follow up assessment. It has been said that the analysis of change in individual goal scores may prevent the loss of important detail regarding goal attainment when average scores are analysed (Damiano, 2014, Verkerk et al., 2021). This is in keeping with the belief that the true importance of any functional change can only be validly

determined at the 'individual level' and its importance related to the individual child and family setting the goal (Stratford and Riddle, 2013).

In this study, individual scores were found to be significantly improved at six weeks post injection and suggested a clinically significant change for both COPM Performance scores and Satisfaction which were maintained at six and 12 months post treatment. This was in contrast with averaged scores where COPM performance scores did not appear to reach clinical significance at six months. Other researchers evaluating the use of COPM in a rehabilitation setting, have also suggested that evaluation of change in individual goal scores can represent a more meaningful reflection of goal attainment than averaged goal scores (Eysen et al., 2011, Vyslysel et al., 2021)

Although goal attainment was shown throughout all ICF domains, an interesting pattern emerged regarding the timing of response. The data suggested that there was a significant improvement in Activity and Participation goal attainment at six weeks post BoNT which was maintained throughout the 12 months. However, BSF and environment goal attainment appeared to show more of a fluctuation in response, although goal attainment was significantly improved at all time points, the greatest improvement was seen at six weeks, with a drop in goal attainment scores between six weeks and six months, which improved again at 12 months.

One explanation for the variation in response within BSF domains could be related to the short-term effect of spasticity reduction. Short term improvement in tone was seen at 6 weeks and this was reflected in improved goal attainment. As expected, there was evidence of a gradual return of spasticity in some children within the study, due to the temporary effect of BoNT-A treatment on muscle tone. (This was also reflected in the lower percentage of children demonstrating a technical response in the muscle at six months).

Once the immediate effects of BoNT-A began to wear off, families may have seen a change in BSF goal performance, such as a gradual increase in the number of trips

and falls in comparison to six weeks post injection, which in turn may have been associated with a deterioration in goal performance as the muscle stiffness had returned. However, by 12 months, goal attainment was once again perceived to improve, independent of the number of injection cycles.

One reason could be that children were more likely to achieve a steady state of motor performance, utilising changes in tone and improved activity at 12 months, and parents and children recognised and acknowledged this as an overall improvement in comparison to baseline scores. This was also observed by Eysen et al. (2011) when describing longitudinal change in COPM scores in the adult population. They suggested that this is most likely due to a re-evaluation of occupational performance taking place, comparing current ability with baseline ability.

Another practical clinical point of note is the relevance of timing at six months. At this assessment time point families are asked about their feelings about the need for repeat injections and in some cases, this may be a driver for families reporting a drop in BSF scores, as this is taken into consideration regarding a child's eligibility for retreatment.

It may be worth considering that although the fundamental aim of BoNT-A treatment is to reduce dynamic spasticity, this is not done in isolation, but as a means to enhance a child's functional activity and improve participation. Therefore, improved activity and participation appear to support the aims of treatment as measured by COPM.

9.4 Participation

CYPwCP can experience greater participation restriction than their peers without disabilities (Palisano et al., 2012). Improved meaningful participation is believed to be the ultimate goal of many interventions in CP, in order to reduce the differences between CYPwCP and their typically developing peers (King et al., 2003). This study used the Participation and Environment Measure – Children and Youth (PEM-CY) to

evaluate change in participation following BoNT-A. The PEM-CY is one of the few paediatric assessment tools that combines the measurement of participation and environment in home, school and community settings and contains a considerable number of participation items that cover all of the nine domains of the ICF-CY Activities and Participation dimensions (Chien et al., 2014). For the purpose of this study the participation related constructs of 'average frequency' and 'average involvement' in functional activities were used to evaluate change in all three settings.

After adjusting for clinical confounders, significant changes were found in at least one of the constructs of participation in all settings following treatment. Nevertheless, change scores were small (0.17-0.44), and it was not possible to judge these changes in terms of clinical importance as MCID values are unknown (Coster et al., 2011).

There was a reported higher frequency of participation and involvement in activities at home following BoNT-A intervention. As the median age of children in this study was 6.5 years (IQR, 5.1-9.6), this may represent a significant improvement in participation for this age group as children would still be expected to spend a large proportion of their time at home.

At school, involvement in school activities significantly improved at six weeks, six months and 12 months in comparison to baseline. However, the only significant increase in the average frequency of participation in school activities was at six months. This was possibly limited by the number of school activities listed in the measure, as increasing these was beyond the control of families and children, such as field trips and attendance at after school activities.

In the community the average involvement in the community activities did not significantly change post injection, this was maybe to be expected as average involvement scores were high at baseline (4.1 out of 5). The average frequency of participation in community activities increased at all time points post injection for the whole group, however a significant difference was observed for children in

different GMFCS Levels. Children in GMFCS II and III participated less frequently than children in GMFCS I (-8.5% and -13% respectively).

Participation is a highly complex individual construct, personal to each child and family with great variability in the meaning to each individual. In reality it may therefore be very difficult to capture change on item-based measures. It remains essential however to attempt to determine whether changes following interventions such as BoNT-A translate into child and parent perceived changes in participation. It has been suggested that the interplay between activity limitation and environmental factors is also important (Anaby et al., 2014, Palisano et al., 2012). Within this study parents' perception of environmental supportiveness in all three settings was relatively high (Home 80%, School 75% and Community 70%) and did not significantly change following treatment. Stability in environmental supportiveness was to be expected as this was an evaluation of BoNT-A intervention with usual care and no specialised intervention was given to improve participation.

The changes observed in this study were in keeping with other interventional and observational studies, in which small changes in average frequency and involvement in participation were also reported (Gibson et al., 2018, Reedman et al., 2019, Valentine et al., 2020a). The changes in participation over time may represent clinically meaningful improvement but identifying what the value is for a clinically meaningful change in the PEM-CY requires further investigation.

Both the CPQOL and PEM-CY questionnaires were developed for use in different countries (Australia and Canada respectively) and although English language is used for the measures, culturally some of the references may be more specific to the country where the measure was developed. This can cause some ambiguity when parents and children are answering the questions. For example, the use of the term 'involvement' in functional activities in the PEM-CY is understandably multi-faceted and this was clarified for the Toxin Study by encouraging parents to think in terms

of their child's 'engagement' in a functional activity. Some parents found the questionnaires challenging *"It's difficult, I can't pretend I enjoy it"*.

Ambiguity appeared to be more apparent in the PEM-CY which was not CP specific than the CPQOL. Some PEM-CY participation activities were particular to Canadian culture, principally with the examples given in the community section, such as participation in religious activities and working for pay and these may have influenced the scoring of this section. Krieger et al. (2020) also identified with some of these challenges when introducing PEM-CY to a German speaking population. There are also cognitive considerations in completing the measure as the test developers suggest that the minimum level of comprehension required to complete the measure is that of a 12-year-old. This was highlighted as a challenge by Srinivasan et al. (2021), who adapted the PEM-CY for use in India leading them to suggest that this *"may preclude its use in cultures with varying educational levels"*. The PEM-CY is a complex questionnaire with a number of parts and the difficulties of completing it were also highlighted by some of the parents during interviews in Phase II *"it's something that you have to really, really read through"*. Several authors have suggested that the PEM-CY could be administered using parent interviews as an improved mode of administration (Khetani et al., 2015, Longo et al., 2019, Srinivasan et al., 2021).

9.5 Quality of life (QOL)

Over the last decades, QOL has become increasingly important to assess outcome following interventions in CP in both research and clinical practice. As with goal setting, the evaluation of wellbeing following an intervention such as BoNT-A is essential in child and family focused practice.

Collecting both self-report and proxy data can help highlight quality of life issues that are most important to CYPwCP and their families (Makris et al., 2021). This study used the parent reported Cerebral Palsy Quality of Life measure (CPQOL) to examine change in health-related quality of life following BoNT-A.

Two aspects of wellbeing related to the Activity and Participation domains were selected, 'Feelings about function' (Function) and 'Participation and physical health' (Participation). As a condition specific tool, CP-QOL incorporates items which are meant to reflect the lived experiences of CYPwCP, including children's and parents' feelings about some of the potentially limiting features of CP, consequently providing a more accurate description of children's HRQoL (Davis et al., 2006, Waters et al., 2006).

In this study after adjusting for all clinical confounders, an improvement was reported in QOL at 6-weeks, 6-months and 12-months as measured by both the Function (6.22%, 5.47%, 4.54%) and Participation (7.87%, 8.62%, 7.53%) domains of CPQOL following BoNT-A. These changes were statistically significantly improved from baseline scores at all time points following treatment.

In the absence of MCIDs it is hard to evaluate the clinical significance of the changes in QOL. However in keeping with the literature where 5% improvement in scores have been suggested to represent significant improvement following an intervention such as Selective Dorsal Rhizotomy (Pennington et al., 2020), this improvement following BoNT-A treatment may represent a clinically significant improvement in both CPQOL Function and Participation scores at 6-weeks and 6-months and Participation at 12-months following BoNT-A.

Few studies have evaluated change in QOL in ambulant CYPwCP following lower limb BoNT-A. However, in keeping with the improvement shown in this study, Dai and Demiryurek (2017) reported a significant short term improvement in QOL as measured by the Child Health Questionnaire (CHQ), comparing two groups receiving BoNT-A with and without casting. Significant improvements in QOL scores were reported in both groups at 6 weeks and these were improved further at 12 weeks post BoNT-A ($p < 0.001$). In contrast Hastings-Ison et al. (2016) also used the CHQ as a proxy measure to assess health-related QOL, comparing two BoNT-A injection frequencies but reported no significant change.

Kelly et al. (2019) used CPQOL to evaluate change in QOL following BoNT-A, evaluating two methods of casting and found no significant improvement in either group at 2 or 6 months following BoNT-A treatment. Thomas et al. (2016), evaluated two methods of physiotherapy intervention, group versus individual following BoNT-A and also found no significant difference between the groups on Function or Participation domains of the CPQOL. It was hard to evaluate change within the groups, as detail was lacking about within group differences following BoNT-A.

It has been suggested that absence of evidence evaluating the impact of interventions in CP might be related to a lack of sensitivity of QOL tools (Davis et al., 2009, Kelly et al., 2019). Parents may express disappointment in the magnitude of change following treatment and this may be reflected in no significant change in QOL outcome (Löwing et al., 2017, Weigl et al., 2007). Others have suggested the ceiling effect of the CPQOL may influence the results especially if there are high scores at baseline (Reedman et al., 2019). This could explain why CPQOL was sensitive enough to pick up change in this study as baseline scores appeared relatively low, 67.5% for Function and 56.7% for Participation. However, a lack of detail about baseline scores in the other studies makes this difficult to confirm, and the absence of MCIDs or score parameters further limits this interpretation.

9.6 Duration of response – re-injection interval

Within this study both statistical and clinically significant improvement in activity measures were observed up to twelve months following BoNT-A after adjusting for clinical confounders. This is in keeping with other research which followed up children beyond six months post injection (Hastings-Ison et al., 2016, Löwing et al., 2017). An improvement in ICF impairment scores was also noted, including a significant reduction in dynamic spasticity (technical response) in the injected muscle, which was still evident for more than half of the children at six months (52%) and 12 months (53 %).

The 24 children who had re-injection within the study period (37.5% of all participants), did so on average 41.3 (SD 4) weeks after the first injection within the study period. This interval was in keeping with other centres who reported longer intervals (9-12 months) between injection cycles (De Beukelaer et al., 2022, Desloovere et al., 2012, Molenaers et al., 2009). This is in contrast to many of the earlier published studies which followed 3-4 monthly injection cycles (Cosgrove et al., 1994, Koman et al., 2001, Wong et al., 2005).

There is increasing evidence to suggest that changes within the muscle following BoNT-A last longer than the 12-16 weeks suggested in earlier studies (Aoki and Guyer, 2001). A number of researchers have demonstrated more long-term changes in muscle histology following a single injection cycle, in some cases over a year (De Coulon et al., 2022, Schroeder et al., 2009b, Williams et al., 2013b). Several studies, including this one, have shown that increased injection frequency does not afford a greater improvement in impairment or activity outcomes (Hastings-Ison et al., 2016, Kanovsky et al., 2009).

Currently, there appears to be a move towards extending re-injection intervals, particularly in the paediatric population. However, it is of note that two recent large RCTs, sponsored by pharmaceutical companies for licensing purposes, described re-injection frequencies in the region of 16 weeks (Delgado et al., 2016b, Heinen et al., 2021). The recent pharma-sponsored 'TIM' study reported re-injection frequencies of 16 weeks in 70.7% of participants, with a mean time to injection of 15.6 (5.2) weeks (Heinen et al., 2021). Delgado et al. (2017b) reported that 74% of their 216 patients required re-injection at 16 weeks in their open label study following their double-blind RCT. Whilst both research groups acknowledged that longer injection frequencies are frequently seen in clinical practice, it may be pertinent to consider that the indication for re-injection was largely based on spasticity measures and not a change in activity or participation outcome.

9.7 Age and repeated injection cycles

At the beginning of this study (2016), international clinical practice was increasingly driven by the adoption of more frequent (four-monthly) injection cycles for younger children as highlighted above. This was based partly on the belief that intensive. (i.e., more frequent) treatment of dynamic spasticity with BoNT-A during the early stages of a child's development could delay contracture development and provide more benefit regarding motor improvement (Graham et al., 2016, Linder et al., 2001, Metaxiotis et al., 2002). This was founded on the seminal work referred to previously by Cosgrove and Graham (1994) which used a hereditary spastic mouse model, when frequent injections throughout the mouse growth period prevented the development of fixed muscle contracture and promoted muscle growth. Consequently, there were concerns that BoNT-A treatment could be overprescribed due to the increased frequency of injection episodes particularly in younger children, with potential harm to the growing muscle.

A number of researchers suggested that younger children benefit from injections more than older children (>8 years) and that treatment should be targeted to younger children between the ages of 2 and 5 years (Franki et al., 2020, Hastings-Ison et al., 2017, Molenaers et al., 2010, Multani et al., 2019a, Papavasiliou et al., 2006, Strobl et al., 2015). Despite this drive to limit treatment to young children, others had suggested that with appropriate patient selection, identifying the presence of dynamic spasticity, older children could also continue to benefit from targeted treatment to improve function and reduce pain. They contended that with accurate patient selection criteria, age was not necessarily a precluding factor (Corry et al., 1998, Franki et al., 2020, Strobl et al., 2015). This is in keeping with the experience in clinical practice; suggesting that appropriate patient selection with an individualised focused approach, incorporating realistic goal setting to optimise outcome, is more important than the age of the child.

Kahraman et al. (2016) suggested that the number of previous injection cycles had an inverse relationship to a positive response to BoNT-A treatment. This together with increasing concern about long term effects on growing muscle, led to a

suggestion by some authors to limit the number of injection cycles (Linder-Lucht et al., 2006, Shortland et al., 2013, Weigl et al., 2007).

In this pragmatic study, which reflected usual clinical practice, there was an opportunity to evaluate the effects of BoNT-A treatment on older children and those who had a varied injection history. This represented a spectrum of children who had BoNT-A for the first time and those who had more than five previous injection cycles.

The data from this study, supported by the use of multilevel modelling to adjust for clinical confounders, suggested that older children who were selected for this treatment often did better than younger children in QFM attributes and activity scores, as well as muscle selectivity, reduced tone and goal attainment. This was partly in keeping with the work of Franki et al. (2015) who found increasing age in their study to be associated with an improved outcome using functional goals (using GAS and GMFM). However, they also found that younger children had more significant reduction in tone, which was not supported by the data from this study.

The number of children in the older age group within this study, as in other CP research, was significantly smaller than those in the younger treatment group. This would suggest that the eighteen children in the older group, (28%), who continued to receive injections were already a self-(and-perhaps-clinician)-selecting group where yearly BoNT-A injections had resulted in functional benefits. They had therefore chosen to continue with treatment with 50% of them having had more than three previous injection cycles.

The results of this study showed that previous injection history did not appear to be significant in predicting outcome in any of the variables measured. Our findings are in keeping with the work of a number of researchers. Schasfoort et al. (2018) found no significant difference in outcome associated with the number of previous injection cycles. Read et al. (2016), in a retrospective analysis of three injection cycles found significant improvement in gait as measured by the Edinburgh Visual Gait Analysis Scale and a maintenance of gait quality in children with equinus after

the second and third BoNT-A injection cycle. More recently Delgado et al. (2017b) reported sustained clinical improvement in hypertonia and goal attainment over a 12 month period following up to four repeat injection cycles.

However, it is challenging to evaluate the effect of repeated injections due to a paucity of longitudinal studies evaluating outcome of children following several injection cycles. Those that do invariably have small numbers of participants making it difficult to draw conclusions. Kahraman et al. (2016), found a lack of information regarding repeat injection cycles in the thirteen studies they reviewed. Based on their results, they could only find evidence to support functional gains following the first two injection episodes and insufficient evidence to review the effect of multiple injections. Evidence would suggest that the majority of children appear to discontinue treatment after 2-3 injection cycles, the reasons may be multifaceted but most likely due to the progression of dynamic contracture to fixed contracture due to the natural progression of CP (Multani et al., 2019b, Weigl et al., 2007).

9.8 Safety

There appears to be a general consensus regarding the systemic safety of BoNT-A treatment within the paediatric population. Kahraman et al. (2016) and Matthews et al. (2016) reviewed data from more than 800 children and concluded from the evidence that BoNT-A treatment was considered safe with a low incidence of treatment related adverse events when injected into the lower limb muscles of CYPwCP. This was confirmed by the data in this study where a small number of mild transient side effects were reported, which were in keeping with other studies in the field (Guyot et al., 2019, O'Flaherty et al., 2011, Paget et al., 2018a). All were completely resolved by the first post injection assessment at 6 weeks.

9.9 Strengths and Limitations

This was a large single site pragmatic mixed methods longitudinal clinical study. The inclusion of outcome measures within all domains of the ICF enabled an evaluation of BoNT-A efficacy in areas considered important to CYPwCP.

Whilst RCTs are frequently considered to be the research design of choice, it has been recognised that mixed methods research may be best placed to evaluate interventions in CP. BoNT-A use is an accepted treatment modality and as such a control group was not deemed appropriate. It is recognised that in the absence of a control group it may not be possible to completely understand to what extent the changes observed within this study are totally attributable to BoNT-A. Nevertheless the robust longitudinal research design ensured that the timing and magnitude of changes in relation to baseline may provide some certainty to the study findings.

This study was keen to evaluate real world 'performance' of pragmatic clinical research, as opposed to the controlled snapshot of 'capacity' as is frequently evaluated in a controlled trial setting. Within this study children had a combination of muscle groups injected which reflects current clinical practice which frequently adopts a multilevel approach (Molenaers et al., 2001). Co-intervention is acknowledged as an essential part of BoNT-A treatment and this was recognised within this study. The reality of clinical practice is that children do not exist in a vacuum and have the complexities of real life representing behavioural factors (such as personality and motivation of both child and family) and environmental factors (such as therapy, recreational activities etc). It is important that research captures real life situations which can advise other clinicians who may be in similar situations with a similar patient group.

There is also the added dimension within the paediatric population of natural growth and development of skills as well as the acknowledged limitations of the progression of musculoskeletal changes in CP. This study has sought to relate all statistical changes to published MCIDs where available, in order to provide context about meaningful practical change in addition to statistical significance.

This is the largest reported study using QFM to evaluate change in movement quality in CYPwCP and to date there has been no published work evaluating QFM's responsiveness to change following an intervention such as CP. The QFM allowed the standardised quantitative assessment of movement quality which was able to

move beyond qualitative descriptions of change in movement quality using 'gestalt' based ratings. In order to minimise bias and ensure robustness of the QFM analysis, the researcher was blinded to treatment order without access to previous scores for each child's QFM assessments.

The results from this study suggest that there was an improvement in movement quality following BoNT-A treatment. The difference between the timing of response for each QFM attribute over the 12-month period was interesting and has clinical implications which can assist in orientating treatment programmes targeting specific areas following BoNT-A intervention.

A strength of the study was the use of multilevel modelling to adjust for clinical confounders in the study. These aimed to address some of the complexities of clinical practice, such as age, GMFCS Level, previous injection history and variety of muscles treated, so that the adjusted effect of time on the ICF outcomes studied could be evaluated. The number of children involved in this single site study was larger than many similar single centre studies in the reported literature following BoNT-A intervention. Nevertheless, the use of multiple models for this number of participants should still be considered exploratory.

Another strength of the study was that data were collected by an established experienced clinical team who followed a standardised testing protocol which has been in use in the clinical setting for 10 years. To ensure reliability in the study assessments the clinical team had two training days prior to data collection commencing and regular monthly reviews with the researcher to ensure protocol adherence during the 18 month of data collection. The data collection did not differ from usual clinical practice.

Limitations

As this was a pragmatic study, children's clinical care followed the usual trajectory including re-injection when indicated. Consequently, there was a variation in the number of treatment episodes each child received within the 12 month study,

which was in keeping with a number of other longer term studies (Delgado et al., 2010, Fehlings et al., 2016, Tedroff, 2009). Whilst this was considered a strength of the study, improving the generalizability of the results to clinical practice, it was also considered an additional confounder and was therefore adjusted for during multilevel modelling.

One aspect that was not controlled for in this study was the therapy that the children received and whilst this was a limitation it was also a realistic evaluation of pragmatic clinical practice. All children received a programme of strengthening and targeted training in functional activities. The study was not designed to compare different methods of therapy, because in clinical practice therapists require flexibility to meet individual children's clinical needs and goals. The minimal level of therapy (4-6 weeks) was met for all children in the study. Usual practice for orthotics and serial casting was followed as determined by the local team.

Measurement tools

Standardised validated outcome measures were used throughout the study. Whilst the aim was to capture children's usual performance, in reality many of the outcomes measured capacity and were unable to capture capability and complex performance, including endurance. This is especially true for the walking tests, whilst tests were chosen for ease and respecting families' time constraints, portable inertial measurement units such as accelerometers and 'Fitbits' may have more accurately measured everyday performance.

The limitations of questionnaires to measure change in participation and HRQoL have been highlighted. Whilst families were encouraged to complete the questionnaires together, there was a limitation in hearing the child's voice directly evaluating treatment as all the study measures were proxy measures. Nevertheless, children's opinions were sought at all assessment time points and during all activity assessments.

Chapter 10 Phase II- Qualitative study methodology

10.1 Introduction

Cerebral Palsy (CP) is a lifelong neurological condition and despite advances in the field, individuals with CP continue to experience substantial barriers to participation in everyday life. Current intervention strategies for CP remain limited (Honan et al., 2022) and interventions often require sustained and significant commitment by families for what is considered by many to be small functional gains (Novak, 2014). Botulinum Toxin A (BoNT-A) treatment is one such intervention and although it is considered an accepted treatment modality for the management of spasticity in children with CP, the benefits on function and participation are relatively unknown.

BoNT-A treatment involves significant commitment from children and families due to the need to repeat injections in some cases two to three times a year and frequent assessments evaluate the need for, and subsequent impact of the treatment (see 4.1.4). Children are often taken out of school for these appointments and parents need to take time away from work. Our aim was to understand the experience of children and their families undergoing BoNT-A treatment and investigate whether standardised assessments, together with current treatment procedures, reflect what is important to children and their families when evaluating the impact of lower limb BoNT-A injections.

10.2 Aim of the qualitative study

The perspectives and experiences of parents and children about their values and beliefs remain largely absent when discussing success of interventions (Rosenbaum and Gorter, 2012). With limited qualitative research in this field, the aim of Phase II was to understand children's and parents' views and experiences of BoNT-A treatment, enabling the final research question in this study to be answered:

“Investigating the experiences of BoNT-A treatment- Do standardised clinical and patient reported outcome measures relate to child and parent perceptions of response following BoNT-A treatment?”

10.3 Design

Phase II was the qualitative component of the concurrent mixed methods study. It encompassed patient centred research, comprising an interpretive descriptive design with semi-structured interviews with children and parents. All the interviews and interpretative analysis were carried out by the researcher (LK) and subsequently the qualitative findings were integrated with the quantitative data set to ensure an integration of all results ensuring true mixed methods research.

An interpretive descriptive design was deemed an appropriate methodological approach, as it was able to address ‘complex experiential questions, whilst producing practical outcomes’ (Thompson Burdine et al., 2021). The primary goal of interpretive design is to address an applied health research question, in this case ‘BoNT-A use in CP’ and create understanding that is of practical importance to the clinical area. It has been described as “an inductive method of qualitative research that involves the formation of a description, but then moves this description beyond the self-evident to further discover potential ‘associations, relationships and patterns within the phenomenon’ (Thorne, 2016) with a focus on bringing the analysis back into the context of the practice field” (Stevenson et al., 2015).

The mosaic approach, combining the ‘traditional methodology of observation and interviewing with the introduction of participatory tools’ was selected to guide interviews with children and young people (Carter and Ford, 2014, Clark and Moss, 2011). This multi-modal approach to data collection is underpinned by the view that CYP are experts in their own lives and should be afforded the opportunity to share their views whenever possible. Within both clinical settings and in research, parents are often consulted on their children’s behalf (Stålberg et al., 2016), which

is not necessarily what families want or what yields the most accurate information (Verkerk et al., 2021). Generating 'real' descriptions of children's experiences, using their own words, was seen as fundamental to this component of the study, ensuring that 'true' results were captured (Bowling, 2014, Rees, 2011). The mosaic approach utilises a toolkit of different creative techniques to ensure that activities are accessible to all participants, acknowledging not only their different skills and personalities but also their cognitive and physical abilities (O'Grady and Dusing, 2015). This was particularly important for children and young people with cerebral palsy who can have a range of physical and cognitive impairments.

Whilst it is important to hear directly from children and young people, the significant role parents have in evaluating interventions for their children was also recognised in assessing realistic outcomes that are meaningful to children and families (Clarke et al., 2016). Including semi-structured interviews with parents ensured that their perspective was also heard (Jette and Haley, 2005).

10.4 Sample and recruitment

A purposive sampling matrix (Mathison, 2005) was used to identify child-parent dyads from the Phase I study sample who were characteristically representative of the study population. A target of at least five CYP was selected from each GMFCS level I, II and III, following review at six months and invited to participate in this phase of the study. It was anticipated that a small diverse sample would be able to provide the depth, complexity and richness of information required for this qualitative element, involving reflexive thematic analysis of the data (Bowling, 2014, Braun and Clarke, 2021b, Carter and Henderson, 2005, Rees, 2011).

In order to ensure a representative sample within each GMFCS level, CYPwCP with *good*, *moderate* and *poor* response to BoNT-A were invited to take part in the qualitative component (see Table 10-1 for predetermined end points). To categorise participants for Phase II of the study, clinicians were asked to evaluate whether there had been a good, moderate or poor response to BoNT-A during the T2 assessment at six months. This was based on the clinician's perception of the

change in dynamic tone (spasticity) as measured by change in R1 on the Modified Tardieu Scale (see 4.2.2).

Response	Summary	R1
Good	Dynamic catch significantly reduced or abolished	≥50% reduction in dynamic catch
Moderate	Dynamic catch partially reduced	<50% reduction in dynamic catch
Poor	Dynamic catch unchanged or increased (i.e. deterioration)	0 < 0 %

Table 10-1 Summary of response to BoNT-A for Phase II

Parents were reassured at each stage that participation in the study would not affect their CYP's access to BoNT-A treatment.

LK contacted families by telephone after reviewing clinic lists and patient notes to identify eligible participants and invited families to confirm their agreement to join Phase II of the study. A convenient date for interview was then arranged by the researcher. A Patient Information sheet (PIS) was given to each family explaining the details of Phase II and a separate consent/assent form was completed prior to the interview for families who agreed to take part (Appendix 14.2). Recruitment continued until there was a balanced group with representation from all GMFCS levels. The first interview took place in October 2018 and the final interview in January 2020. The delay in recruitment was associated with an overall delay for the study of recruiting children in GMFCS Level III.

10.5 Semi-structured interview schedules

Interview schedules were developed by the researcher following training in the mosaic approach and coaching in interview techniques. The key areas to explore during the interviews were identified for both children and adults, reflecting gaps in the existing research and supported by expert members of the supervisory team (KO) with expertise in qualitative research.

Priority was given to questions exploring CYPwCP and parent attitudes and experiences related to their most recent BoNT-A intervention. This involved

evaluation of the procedure, exploring the impact of treatment and changes that were important to children and families. However, interview schedules were also designed so parents and children could share their experiences about any stage in the procedure of receiving BoNT-A injections. These also included specific prompts to help encourage more in-depth conversation when required (CYP- and parent/carer-specific- see Appendix 14.5).

Interview schedules were modified following consultation with the study steering group, comprising two CYPwCP and their mothers. The steering group members met in person and provided feedback on the overall content of the interview schedule, as well as commenting on specific wording and methods of engaging families in the interview process.

They suggested that parents and children should be invited to 'chat' or 'talk' about their experiences, rather than be 'interviewed'. 'Interviews' were deemed by the study steering group to be too formal and could be considered intimidating for some families. The children from the study steering committee in addition to two young children aged 5 years and 12 years (one child with CP and her typically developing sibling), were also consulted about the different methods to be used in the Mosaic approach, such as use of playmobil™, drawing and postcards in order to confirm their suitability for children and young people. A number of extra figures were added to the toys available, such as spiderman to broaden the appeal to young children. Each child was given a personalised certificate of thanks and a choice of stickers following the interview (Appendix 14.5).

The refined interview schedule was sent for review by the hospital Young People's Advisory Group, (YPAG) which comprises a diverse group of children and young people receiving treatment at GOSH for a variety of conditions. A short explanation of the main topic areas and information that the researcher wanted to gain from the interviews were provided to the YPAG, who were asked to comment on the wording and content of the proposed interview schedules for both adults and children.

The importance of gently easing families into the subject of BoNT-A treatment was highlighted by both groups, as well as providing opportunities for them to talk about what kind of activities they/their children liked to do and allowing participants to elaborate on the impact of BoNT-A on different areas of their own/child's life. These were subsequently emphasised in the interviews.

All interviews were carried out by the Researcher (LK). Questions were asked in an open manner to encourage conversation and explore the interviewee's own thoughts rather than be directed by the researcher. Using this approach offered the opportunity to investigate the experiences of both children and their parents, allowing a description in their own words, ensuring that the true results were captured (Horstman et al., 2008). Conversation continued until everything on the topic guide had been discussed, or children and parents did not wish to say anything further.

To aid recall, interviews with parents initially focused on the child's most recent BoNT-A injection and experience of the procedure, with prompts to explore how this treatment may have impacted on a child's activity and participation opportunities (drawing on the ICF framework to facilitate discussion). Any concerns about the assessment and injection procedures were also discussed. Parents whose children had undergone more than one injection were asked to think about how their current experience differed or was the same as previous injections. Parents and children were also encouraged to think about advice they would give to others about undergoing BoNT-A treatment.

Families were given a choice between interviews taking place at the hospital or in their own home, however, all parents chose to be interviewed at the hospital whilst attending for another appointment. Whilst parents were offered the choice of being interviewed separately from their child, all chose to be interviewed with their child playing beside them. Similarly, all children chose to have parents with them throughout their interview.

A choice of different data collection activities was available to facilitate interviews with children about their experience of BoNT-A injections. Third person reporting was encouraged in order to reduce any potential bias that might have occurred from the families knowing the researcher (Oulton et al., 2017). These included: writing a letter to a friend who was about to have injections and asking the child to 'give them top tips'; a 3rd person craft activity using a cut-out cardboard figure of a child about to have injections for the first time; and structural play using playmobil™ set up as an injection room in the hospital. Children could choose any activity and move between activities as they wished (see Figure 10-1). The process started with CYP being asked how they would describe having injections to their friends.



Figure 10-1 Examples of craft activities for interviews with children

The interviews were audio recorded with permission from participants using a 'jigmo' encrypted digital voice recorder. Recordings were labelled by [Toxin_study_

participant number], downloaded and stored as Windows Media Audio files in a password protected storage folder on a hospital computer. Interviews were transcribed verbatim by a professional transcribing service (TAKENOTE™), stored by participant number and entered into a password protected database for analysis. Each transcript was validated by LK to check accuracy and completeness.

10.6 Data Analysis

Data were analysed using reflexive Thematic Analysis (TA) and followed Braun and Clarke’s suggested six phase framework summarised in Table 10-2 (Braun and Clarke, 2006, Braun and Clarke, 2019, Braun and Clarke, 2021a). The six-phase framework allowed interrogation of the data, patterns in the data were explored and themes were generated regarding the experience of BoNT-A treatment and its impact on children’s lives. The powerful information generated enabled insight into how closely the standardised outcome measures related to families’ experience of treatment. The results from this chapter are discussed in relation to the results from Phase I of the study (quantitative data) in Chapter 12 (synthesis chapter).

Step 1. Familiarisation with the data	Step 4. Developing and Reviewing potential themes
Step 2. Generating initial codes	Step 5. Refining, Defining and naming themes
Step 3. Generating initial themes from coded and collated data	Step 6. Write -up- producing the report

Table 10-2 Six phase framework of reflexive thematic analysis (Braun and Clarke, 2019)

The interviews were transcribed, and the anonymised transcripts were thoroughly read and re-read several times. The researcher (LK) coded the original transcripts and additional initial coding was also done by the supervisor (KO). These initial codes were discussed and reviewed in order to ensure the credibility of the findings acknowledging both the effect of the researcher’s familiarity with the families on analysis as well as the supervisor’s independence from the data. Quality of coding in reflexive TA is not believed to stem from ‘consensus between coders, but from depth of engagement with the data’ and it is based on the reflexive process (Braun and Clarke, 2021b). This resulted in enhancement of the analytical power and

brought in different issues which helped to ensure the data was interrogated in a richer way (Braun and Clarke, 2019, Braun and Clarke, 2021a). The trustworthiness of the results was addressed in that both LK and KO took an active part in the analysis of the data. The analyses were discussed in several meetings, and the construction of codes, categories and themes was decided upon through agreement between the researcher and supervisor (LK and KO). Quotations from the interviews are used to illustrate the categories.

An initial search of the data resulted in the generation of initial codes. Data were not coded to fit a pre-existing coding framework but were instead ‘open-coded’ in order to best represent the meaning as communicated by parents and children in the interviews (Braun and Clarke, 2013). These codes allowed categorisation and exploration of patterns leading to development of initial themes, these were then reviewed and refined (Appendix 14.10). This approach enabled categories and themes and a final narrative to be generated inductively from the experiences of both parents and CYP in order to answer the research question (Figure 10-2).



Figure 10-2 Reflexive Thematic Analysis (Braun and Clarke, 2019)

The researcher moved between different physical spaces when interrogating the data. Using different environments provided a conscious change in mood and ability to analyse the data. It was not a linear process but a recursive process between text codes and themes. This change allowed modification of the researcher's analytical sensitivity and interpretive responsiveness to the data (Braun and Clarke, 2019, Byrne, 2021). Themes were revisited, refined and defined. The themes generated reflected the researcher's interpretive lens and are supported by direct quotes from the transcripts (see Appendix 14.10 for examples of coding and theme generation).

Whilst a predominantly inductive data driven approach was adopted in this study, there was also a degree of deductive analysis employed to ensure that the coding contributed to producing themes that were meaningful to the research question (Byrne, 2021), and also to ensure that the parent and child meanings that were highlighted and emphasised from the data were relevant to the research questions.

It has been suggested that what is relevant within the data is not always apparent within the themes chosen by professionals (Peplow and Carpenter, 2013).

Therefore, the final themes were shared with a family from the steering group (mother and son), as a form of 'proxy member checking'. The family recognised and identified with the chosen themes and confirmed the importance of experiences raised within the data, both of them believing that the themes mapped onto the assumptions they held about their experience of BoNT-A treatment.

Chapter 11 Results of Phase II

This chapter summarises the results of the thematic analysis of the interviews with parents and children. Firstly the demographics of the Phase II sample will be presented with information about administration of the semi-structured interviews. This will be followed by an in-depth analysis of the rich data provided by families and the themes identified within the data explored.

11.1 Phase II study demographics

Purposive sampling was used to identify 18 child-parent dyads from the Phase I study sample who were characteristically representative of the study population. There were no significant differences in age, GMFCS level or number of previous injection sessions when compared to the total sample. All parents who were invited to participate in Phase II agreed to be interviewed.

Administration details

Due to the semi structured design and mosaic approach for children, interview length varied with each family. The shortest interview was 30 minutes and the longest 65 minutes, with a mean time of 55 minutes.

The first four children interviewed were under 6 years of age (all girls). During these early interviews the girls were very absorbed in the craft activities with few comments made about their BoNT-A experience apart from the individual recollection of the injection experience. In subsequent interviews, the researcher used more structural play using playmobil, setting up a 'clinic room' to aid discussion about the BoNT-A experience and allowed CYP to carry on with the craft activity whilst interviewing the parent (see Figure 10-1).

Direct quotes have been used to provide evidence of the themes and support the findings. Quotes are denoted in italic text, followed by details of the origin of the quote (e.g. [99,F,5,I,F_M]). This includes a unique participant identifier, child's

gender (F=Female, M=Male), age (years) and GMFCS category (Level I, II or III) followed by interviewee (F= father, M= mother, C= child) and clinicians impression of response (G= Good, M=Moderate P=Poor) in order to trace back to coding for complete transparency and theme level coding.

The demographics of the Phase II sample are summarised in Table 11-1.

Baseline characteristics of participants for Phase II	n
Study participants (Female/ Male)	18 (11/7)
Parent-child dyads	
Single parent (mother/father)	11(11/0)
Both parents	7
Cerebral Palsy distribution	
Unilateral	9
Bilateral	9
Dominant tone presentation	
Spastic	3
Mixed spastic/dystonic	15
GMFCS Level (Responder: Good/Moderate/Poor)	
GMFCS Level I	7 (4/3/0)
GMFCS Level II	6 (1/2/3)
GMFCS Level III	5 (1/2/2)
Responder: (GMFCS Level I/II/III)	
Good	6 (4/1/1)
Moderate	7 (3/2/2)
Poor	5 (0/3/2)
Age years	
mean (SD)	7.4 (2.8)
Range (SD)	4.2-12.5
Age Strata	
4-8 years	14
9-18 years	4
Co-morbidities (Learning difficulties/Autistic Spectrum Disorder)	8 (7/1)
BoNT-A treatment	
Median number of injection sessions (25 th ,75 th)	2.5 (1,3.3)
First injection (Toxin naïve)	9
Second injection	4
Third injection	3
Fifth injection	1
Seventh injection	1

Table 11-1 Demographics for participants in Phase II of the study

11.2 Summary of the Thematic Analysis of Phase II interviews

An overarching theme of uncertainty and anxiety was generated from data from the parents' interviews. Uncertainty was expressed not only in relation to the BoNT-A treatment process but also regarding their child's diagnosis of cerebral palsy and what this meant in reality for their everyday lives.

Underpinning the central theme were six interlocking subthemes which have been summarised in Table 11-2.

Sub themes	Categories
Drivers for treatment	Uncertainty about the future- anxiety about doing the right thing?
Botulinum Toxin A	Uncertainty about the effects of the drug and anxiety about the injection procedure
Engagement	How to manage uncertainty and anxiety, what works what doesn't.
Impact seen through the lens of the ICF	Uncertainty about how it will really affect children's lives
Managing expectations	Uncertainty about how children will respond -The good the bad and the ambivalent.
Measuring Outcome	Uncertainty- should we do it again?

Table 11-2 Themes and sub-themes generated from the data

The process of data reduction has been illustrated in the thematic map shown in Figure 11-1 and each of the subthemes will be discussed in turn in the following sections.

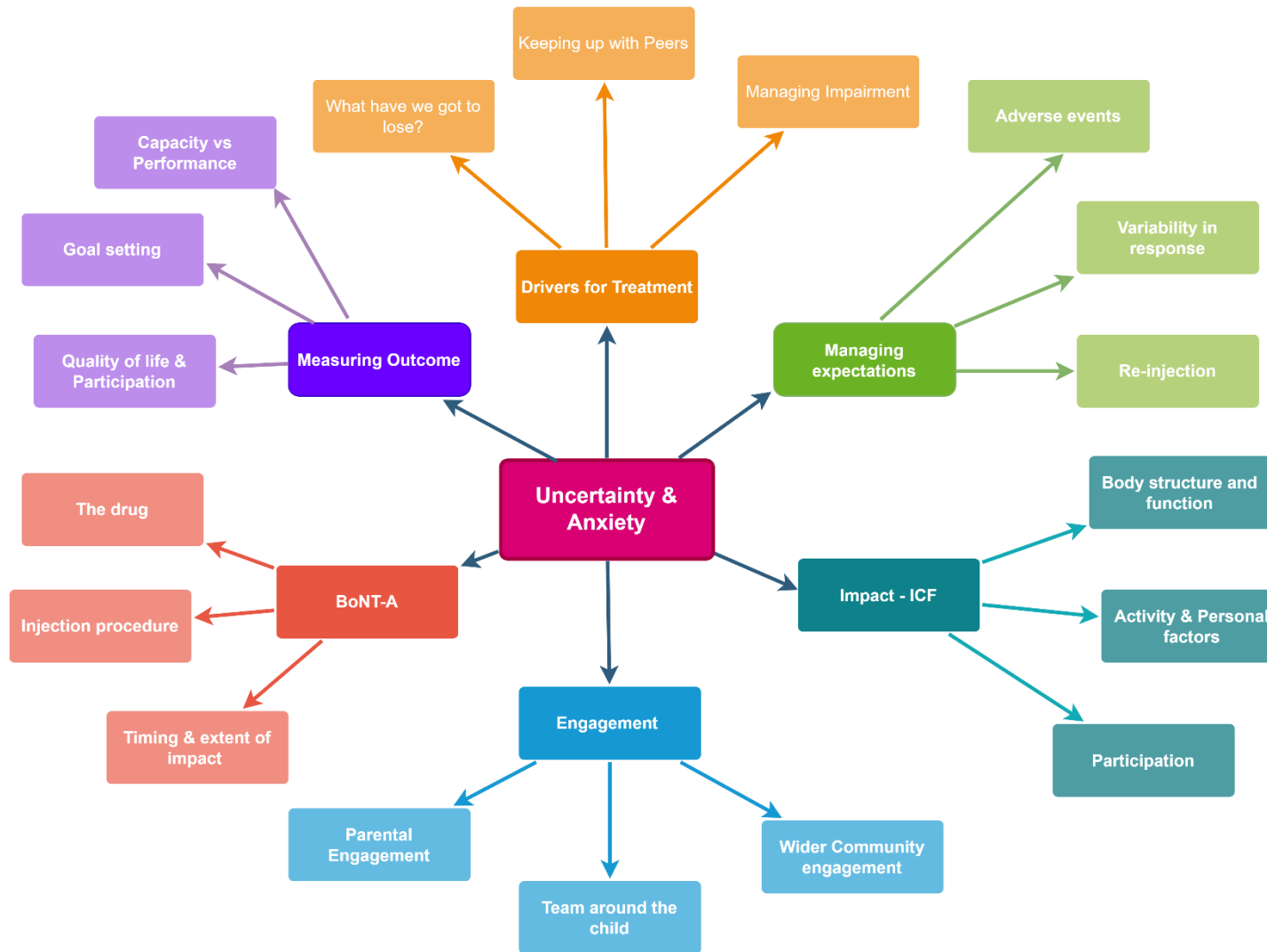


Figure 11-1 Final Thematic map based on Braun and Clarke (2019)

11.3 Drivers for treatment

“When you've got a child with cerebral palsy you are so desperate for that child to run around”

Interviews did not focus directly on the trigger for seeking BoNT-A treatment, but did nonetheless reveal some of the reasons why parents chose to undergo this relatively invasive procedure of multiple injections for their children. These were described in relation to three specific areas:

- Physical symptoms, managing pain and impairments associated with CP
- Parents' desire for their child to keep up with their peer group
- Parents' feeling the need to intervene in some way to help their child and minimise the effects of CP.

A consistent thread was parental uncertainty about their child's future living with CP. Uncertainty about knowing the best thing to do for their child but feeling like that they had to *try* something. Many parents expressed the feeling of having nothing to lose from their child trying BoNT-A injections. Further uncertainty was highlighted around the subsequent decision making about putting their child through more injection cycles.

11.3.1 Managing pain and symptoms

In some cases, parents described how their child's physical symptoms pre-injection had led them to seek treatment. Often the reason for seeking treatment was inferred, but most frequently success of BoNT-A treatment was measured in terms of activity and physical symptoms:

She can go longer now; she doesn't get pains in her legs.

[37,F,5,I,F_M]

This father described his daughter's increased walking distance following injections due to less pain. Similarly, another parent enthusiastically recommended BoNT-A to other families as her son had experienced relief from pain caused by stiff muscles:

If their legs are really tight or ... part of their body's really tight, and they're finding difficulty within pain. I would definitely recommend it. [56,M,9,II,M_P]

The encouragement for other children to try injections was also reflected by a mother of a four-year-old girl, whose daughter had injections for the first time. The family had hoped for relief of her physical impairments, but also described improved mobility as an unexpected 'bonus' following treatment:

It's always worth a try and I would recommend [it]... you've got the bonus of getting some mobility back [66,F,4,III,M_P]

Often there is a degree of uncertainty about treatment outcomes and what parents can do to manage their child's disability, as highlighted in the above quote. In the case of this family, they were keen to try injections considering it 'worth a try' as doing nothing was not an option for them.

11.3.2 Keeping up with peers

Whilst relief from physical symptoms were highlighted by some parents as an important driver for seeking BoNT-A treatment, another key motivation for treatment was to improve mobility and help children keep up with their peers.

Parents understandably compared their child's physical progress with their typically developing peers, expressing uncertainty and anxiety about what the future might hold. In order to facilitate their child's inclusion in the wider community, they were willing to intervene in any way possible to help their children and minimise the effects of CP.

Parents strived for children to realise their full potential and fit in with their peer group, as highlighted in this quote from the mother of a four-year-old with limited motor ability who walked using a walking frame:

You are so desperate for your child to have a full life for me the participation outweighs everything [66,F,4,III,M_P]

Interacting with typically developing peers, particularly within physical activities such as Physical Education (PE) lessons or in the school playground can often highlight to parents and children alike the extent of the disparity in their motor ability in comparison to their friends. As this mother pointed out, the school day can bring added challenges for a child with CP:

How they fit in at school and whether they're able to keep up in P.E.... Emotionally, it's that you really don't want them to feel left out in any way [5-year-old girl, GMFCS I][1,F,5,1,M_G]

This mother's quote also highlights the emotional challenges that parents can face when observing their children not keeping up physically, as well as alluding to the emotional struggles the child may encounter.

Parents frequently seek treatment at specific milestones and transition points in their children's lives, with the concept of 'fitting in' repeated in several different accounts. Starting school for the first time appeared to be a particular 'touchpoint', as a mother whose child had limited motor ability (GMFCS III) explained:

I wanted it done before school so that when she went into school she didn't feel as restricted, which seems to have worked.
[70,F,4,III,P_M]

In this case the timing appeared to work well, improving her daughter's motor ability at the right time for her. This has implications for practice when thinking about how much clinicians allow families to control the timing of BoNT-A injections.

Acknowledging a parent's expertise about the best time for treatment may help reduce anxiety and stress for families.

The theme of 'fitting in' and 'keeping up' appeared to become even more important as children grew, and their physical differences became more obvious. Parents were increasingly aware of their children being 'left behind', cognisant of the gap between them and their typically developing peers widening.

The issue of being different from their peers was highlighted by many parents. This appeared to become more distressing for children as they become increasingly aware of their own reduced motor ability and in many cases increased muscle stiffness:

As he's getting older, he's noticing the difference a bit more, so it is getting a bit harder, because he's a bit behind I suppose. But he still tries to join in and tries to keep up. [19, M, I, 6, M_M]

This mother reported being prompted to seek BoNT-A treatment for her six-year-old child in response to things 'getting harder' for him.

The driver for parents to improve their child's motor ability was not solely related to physically keeping up with their peers but also about ensuring that opportunities to socialise and make friends were not compromised:

She's got to live with it [CP] her whole life. So, it's about her having a positive attitude towards it. It's really important. Because they're going to have to maintain it for their whole life, and it shapes who they are. A big part of it, also, is the social side of having cerebral palsy, because you might not interact with others as much because you just don't physically put yourself into those spaces. [16,F,4,I,M_G]

This quote highlights particularly well the pressure on parents to prepare their children to live with a 'lifelong' disability within today's society, and not let physical restrictions limit them or inhibit their opportunities to participate.

It was apparent that the desire for some children to physically fit in with their peers could lead them to increase their risk of injury. This was highlighted by one mother who shared that whilst she was grateful her son could walk, his yearning to fit in brought about its own complications:

Yes, I'm upset. I've put a lot in ... you know, he can walk, so I'm grateful for that, and he's really determined as well. Like, he hasn't really been using his frame in school because he doesn't want to be different. He says he does fall over and stuff. He hasn't got very good balance, but it does make me sad to see the way he's walking because it's worse now, when it shouldn't be really ... It is affecting him quite a lot. He feels left out. [59,M,6,III,M_P]

As in the case of many of the parents, increased impairment and activity limitation in her son prompted this mother to seek treatment, ultimately to avoid him being socially excluded. The situation was clearly emotionally difficult for the mother and the child and highlights the multi-faceted challenges which families experience.

A number of parents talked about their children's feelings of frustration particularly in relation to their tight muscles and inability to walk independently. The physical consequences of not being able to keep up, did in some cases, cause children to 'self-harm' out of frustration. One father of a child with a more severe motor impairment described how BoNT-A injections had a positive effect on this aspect of his daughter's behaviour:

The only thing she ever asks me is why doesn't my legs work? ... Because the frustration when she would hit herself in the head, it's like her head didn't work and she'd slap her head to make her head work. She hasn't done that for months now. [66,F,4,III,F_P]

This quote highlights the distress some children experience when they realise that their bodies don't work in the same way as their friends. This underlines the extent of the emotional as well as physical challenges children with CP may be facing when families consider BoNT-A treatment.

Several parents shared the challenges regarding their child's changing attitude to their own disability. It was apparent that a desire to keep up with peers changes with age as does their frustration with their own lack of mobility. This was often provoked by increased contact with children and adults outside the immediate family and friendship circle, such as when starting school:

This is the age now where he's starting to notice. Like, before, it never really bothered him, but he's now, noticed that there are things that his friends do that he can't do and he does get very angry, very frustrated. [51,M,5,II,M_G]

The physical limitations have had a negative effect on this five-year-old boy's emotional well-being and his mother identified his lowered self-esteem and anger as a driver for her to seek intervention to help with her sons' walking ability.

The emotional impact of children keeping up with peers was re-iterated many times, giving insight to the emotional distress of the parents as well as the child seen through the parents' eyes, as illustrated in this quote from a mother of a four-year-old

When you've got a child with cerebral palsy you are so desperate for that child to run around with her peers and have a full life, because children don't stop, they will run and expect you to run .. and if you can't keep up, which she couldn't do, she would just sit in a corner with her head dropped. So, for me participation outweighs everything. [66,F,4,III,M_P]

In this example, this mother expressed the extent of the emotional impact of her daughter not fitting in with her peer group at four years of age. She sought out treatment because she was willing to try any opportunity to improve her child's participation and sense of belonging with her peer group.

The data highlighted the interplay between impairment at the level of body structure and function and reduced motor ability, which could subsequently limit participation. Parents shared their concerns about reduced mobility adversely affecting their child's emotional wellbeing. As highlighted earlier if you "don't physically put yourself into those spaces" the interaction can't happen between children and their peers. Important opportunities to socialise can be missed.

11.3.3 What have we got to lose?

Many parents highlighted the desire to intervene to help relieve their child's physical impairments associated with having CP. They described the need to just 'do' something, despite uncertainty about whether treatment options, such as BoNT-A, would work and were safe:

You don't know something's going to work unless you try it, and if it doesn't then you don't do it again. But ..., you know, if they get harmed in the process, and it makes them worse, at least you've done it with the intention that it was going to make them better, if that makes sense. [59,M,6,III,M_P]

Despite this mother, and other parents, taking a very pragmatic approach to trying new interventions, others did acknowledge the reservations and concerns they had about having to put their child through repeated injections:

It's never an easy decision to put your child to have more injections in their leg and all of that, but there's no downside and I think that's the important thing. We've seen nothing that's negative from the Botox. [66,F,4,III,M_P]

This quote provides insight into the potential dilemmas parents face when having to decide whether or not to continue treatment. As this mother concedes it's not an easy choice, balancing continued treatment and potential discomfort of more injections with close evaluation of continued benefits for her child. In this family's case they had not seen any harm.

However, this contrasted sharply with another mother's experience which had not been as positive and had resulted in little benefit for her daughter:

Although we didn't want to put her through it, if it was going to benefit her then it was worth putting her through that. And after this second time, I was like I'm never doing that to her again because it didn't [benefit her] [60,F,6,II,M_P]

The data reinforced the challenging parental role of repeated decision making about choosing interventions which will impact on their child's care. This element of uncertainty and pressure on parents to make a decision about treatments with a variable response can result in anxiety for families and guilt if there is no perceived benefit.

What was apparent was that parents were faced with uncertainty about the likely impact of BoNT-A treatment on their child. The decision about whether to embark on treatment appeared to be a balance of parents' experience of the perceived benefits of treatment. Parents relied on the experience of others to help make their decision and in turn shared their own experiences to support other parents:

Hundred percent, hundred percent.... It's always worth a try and I would recommend everyone, the same way we've since met parents who've had Botox and they recommended it
[66,F,4,III,M_P]

Many parents stressed the variability in response and the differing impact of injections on different children, acknowledging that each child is different. Parents,

despite encouraging other parents to ‘give it a go’, also shared their own experience that BoNT-A wasn’t necessarily the ideal treatment choice for all children:

Every case is different with cerebral palsy. If you've got a mild tone, then I'd definitely give it a go. But if you've got extreme tone, I wouldn't bother. [60,F,6,II,M_P]

The data revealed the degree of pressure and the amount of responsibility placed on parents to decide not only about initial BoNT-A treatment but also whether to continue with subsequent treatment episodes. The mother in the quote above was rather disillusioned as she had put her child through a second set of injections that didn’t work but nevertheless it didn’t stop her advising other children to try it, adding the caveat that if muscles were too stiff there was an uncertainty as to the degree of response and personally, she ‘wouldn’t bother’.

In contrast one father, who as a healthcare professional was perhaps more aware of the conflicting evidence surrounding the benefits of BoNT-A injections, shared his opinion:

On balance looking at the evidence, as long as injections influence function I would recommend treatment Any improvement in function is valuable for any child, any improvement is a difference that's appreciated [64,F,7,II,F_M]

This example highlights that parents may be willing to opt for treatment often expecting only small gains, as any potential functional gains are worthwhile. This was confirmed by other parents, including this mother of a five-year-old girl who revealed that changes are often subtle and offered this advice to other parents:

I'd think don't expect a miracle.... Even if it didn't change that much, I'm still glad we did it. [63, F, 5, II, M_M]

This quote re-iterates many parents' underlying philosophy of 'what have you got to lose?' when choosing injections for their child. Despite some parents' uncertainty about the efficacy of BoNT-A prior to treatment, the overriding theme from the data was the strength of parents' willingness to try BoNT-A to improve their child's condition.

Parents sometimes had low expectations for success, framing their response in realism when expressing their disappointment with the treatment:

I didn't really understand how a needle was going to make a change in his leg. To begin with, to be honest. I did have a bit of hope, but I wasn't expecting that because I just thought his leg was just past that point anyway, to be fair. [59,M,6,III,M_P]

Other parents were hopeful for treatment success despite being realistic about the potential for treatment success:

We knew it was only a 50/50 chance of it working...Yes, because they said her muscle tone was very extreme. [60,F,6,II,M_P]

This highlighted that parents could still choose an intervention even when the outcome was relatively uncertain. In the absence of a 'cure' it has been said that parents are willing to try treatments if they believe there is a chance it will improve their child's activity and the ultimate goal of improved participation (Honan et al., 2022).

Parents also shared concerns about treatment eligibility. Despite wanting to 'give it a go', in some circumstances, they felt judged about the mildness of their child's physical impairment. Some families were uncertain as to whether permission for treatment with BoNT-A injections would be granted. This quote, from a parent whose daughter had 'good' motor ability and could walk independently without the use of aids (GMFCS Level I), highlights this point particularly well:

The consultant said because she's mild, the changes and what will happen to her, are almost too mild to be treated on the NHS. She just said it. I wasn't pressuring her or anything. I was just like, what's the plan or whatever? But that's what she ended up saying ... the next child came in with a big frame. So, I know that's just what they're, sort of, focussing on... But the thing is, it [botox] made such a difference for her.[16, F,4, I,M_G]

This example, amongst others, highlighted a parental perception of a 'hierarchy of disability', in some cases dictating whether one child was more 'deserving' of treatment than another child with CP. This mother expressed her frustration in relation to this, especially as injections did make a difference to her five-year-old daughter. Another parent framed this sense of hierarchy in terms of being 'grateful' that her child was able to access treatment when her condition was considered so 'mild':

I think the cases like her, I can so see how that would just slip through totally.....I think also that even something as advanced as a Botox injection is even available for something like this was just really encouraging..... so we are a massive advocate..... We are really, really pleased with the results, so for us it's made a massive difference [1,F,5,1,M_G]

This quote illustrates the significance of a positive response to BoNT-A treatment 'even' in a child with a relatively mild motor impairment (GMFCS I) and provides a window on some of the complexities of decision making around what treatment interventions are deemed appropriate for different levels of disability.

11.4 Uncertainty about treatment Botulinum Toxin A

Botulinum Toxin has been classified as 'one of the most potent neurotoxins known to man' (Lamanna, 1959). Despite the fact that parents were willing to 'give injections a go' as highlighted in the previous section, understandably an element of

uncertainty regarding the use of BoNT-A as a treatment intervention was present in parents' interviews. This uncertainty resulted in a heightened level of anxiety for many families. Some parents expressed feelings of anxiety related to all three stages of the treatment; before injections when considering the use of BoNT-A- the drug, the injection procedure itself, and following the injections, both in the immediate period post intervention but also when considering further injections once the effects of the injections had worn off.

Parents were uncertain about whether they 'were doing the right thing'. They stressed the importance of other people's support in helping them prepare their child for a positive injection experience, particularly the professionals in the clinic. This mother emphasized the role of the adults around the child and their behaviour being paramount in shaping the experience for the child, making it a 'big deal or not':

It's how the adults around you behave, really effects if it's a big deal, making it a big deal or not. [16,F,4,I,M_G]

She described the importance of adults' roles in making any intervention a positive intervention. She went on to highlight that providing information about the practical details of the procedure would have helped them as parents prepare their own child. This mother urged the clinicians in the service to share other children's experiences following injections, especially for those receiving injections for the first time.

Because you've seen so many cases and you've seen the different things, that's so helpful for a parent because we are only experiencing it with this child, so we really don't know.

[16,F,4,I,M_G]

This quote highlights the importance of personal detail for families when seeking reassurance for treatment choices (nomothetic versus idiographic knowledge (Ashworth et al., 2019)). Professionals have a responsibility to try to alleviate

parental uncertainty by providing as much information as possible to families, based not only on their generic experience as clinicians, but individualised first-hand accounts from families.

Some parents voiced uncertainty about what to expect from the treatment and were unsure about what injections could do for their child. This was the case with one mother who revealed that she had no preconceived opinion about what would happen before her son's first treatment as *"there was no point of view"*:

I didn't really know what to expect. It was just a wait and see sort of thing. [56,M,9,II,M_P]

However, uncertainty didn't just affect the immediate family, as one mother explained:

School also, they didn't know anything. They were like, 'Oh, she's going to have this done. We don't know what that's going to be at all.' [16,F,4,I,M_G].

More information would have helped her to advise school staff and other family members involved in her daughter's care:

So, that would've been helpful ... maybe if you just say, 'This is what the experiences of other people are.' That really helps you, as a parent, to plan and to know [16,F,4,I,M_G].

This quote highlights what parents can find helpful when managing uncertainty and the resultant anxiety arising from this (further examples of family engagement will be explored later in section 11.5).

11.4.1 BoNT-A -The drug

Understandably there were concerns expressed by parents about the injections and injection procedure. This was multifaceted, as there was uncertainty expressed

about the effects and potential danger of the drug product, the process of injecting a known toxic substance into their child's muscles, and the potential need for multiple injections.

Parents were keen to do the right thing for their child, but one mother expressed her anxiety regarding BoNT-A:

I didn't really understand what Botox is, you know. It's a toxin which doesn't sound very good does it? So, it is a bit worrying as a parent, I was quite worried on that aspect. [63,F,5,II,M_M]

This mother's fears had been alleviated somewhat by information provided but she was mostly reassured by the fact that the treatment had been recommended by professionals in the clinic. However, a degree of hesitancy was still evident in the language used:

I was given a couple of leaflets to read and stuff. That sort of helped ease my mind a bit and I felt because that was what we've been recommended, so obviously, it can't be all bad, if they do that. [63,F,5,II,M_M]

Parents also expressed uncertainty about potential side effects of the drug, which are listed in some detail before a child's first injection session:

You don't know what the side effects are.... they said something about they can lose control of their ...bladder. [70,F,4,III,P_M]

An element of uncertainty is necessarily introduced with the consent process when preparing children for injections and warning of the side effects. However, it was also apparent that anxiety was heightened in families when they considered there to be a 'lack of transparency' and uncertainty about what would happen during the procedure and the effects afterwards, as highlighted in this case:

So, we didn't know what to expect ...he kind of said that it might be an overdose the first time because you 'don't know how much you're giving', but you are cautious. I felt like there wasn't that much information, actually, about that process at all ... Each case is different, but it means that you're not prepared as a parent for what will happen [16, F,4, I,M_G]

The use of emotive words such as 'overdose' and a perceived lack of accuracy by the professionals 'you don't know how much you're giving' highlights the degree of heightened anxiety for some parents. This was particularly pertinent for children having injections for the first time, as well as the significant role that professionals can play in accentuating or alleviating parents' concerns. This quote reflects how in this case, the family were not provided with enough information at the time and at a level appropriate to their needs.

The data also highlighted that not all parents expressed the same anxiety when choosing BoNT-A as a treatment option. One mother explained that her fears regarding the risks of treatment were allayed following information from her local medical team:

Our paediatrician always told us about the Botox [BoNT-A]- it's not really a high risk thing, so erased any fears. [66,F,4,III,M_P]

This quote from the mother of a four-year-old girl gives some understanding into the decision-making processes that parents go through when considering interventions for their child. Families do share information with each other, do their own research and weigh up what they know about the perceived risks. However, in many cases, they are still very reliant on professionals providing information about treatments. As in the case of this family, their perception of risk of the treatment was shaped by the professional.

In the case of this family and several others it was apparent that the decision to opt for BoNT-A was in the context of it being a relatively 'low risk' intervention

compared to an irreversible procedure such as orthopaedic surgery. Another mother whose child was listed for a surgical review was not concerned about injections in the same way as she was about the operation:

It's actually the physical operation that always worries me more than the actual giving of the injections. Whether it's going to be painful, whether she's going to be in distress [66, F, 4, III, M_P]

This quote illustrates how aware parents are of the hierarchy of interventions that their child may be offered.

Parents did express concern about the long-term effects of BoNT-A treatment and the uncertainty about repeating treatment. Concern was expressed by one mother in relation to the long-term effects of injecting BoNT-A into her child's growing muscles. This quote highlights the apprehension about what that this might mean for her child:

It's a shame there is no long-term scale of how it affects you later on life ... that is the downside [of BoNT-A], [66,F,4,III,M_P]

However, she went on to rationalize any concerns she may have had regarding the long-term effects of injections for her daughter by outweighing them against any opportunity to improve her child's participation and sense of belonging with her peer group:

For me the participation outweighs everything, you are so desperate for your child to have a full life [66,F,4,III,M_P]

This also underlines the struggle that parents often face having to make challenging decisions about treatments which could affect their child's future health, weighing up the impact on different areas of their child's life.

11.4.2 BoNT-A -The injection procedure

The administration of injections, in a day case setting with sedation, understandably resulted in an element of uncertainty for parents. This included apprehension about what would actually happen on the day, as well as any pain or physical symptoms their child might experience following injections. This led to some families expressing anxiety about what their children would go through, with one family reporting that they had no idea what to expect when their child received injections for the first time:

We didn't know what to expect, and we didn't know if the day after she had it, she'd be in a lot of pain from deep muscle injections, or if she'd go all wobbly and that would have a quick effect because you'd have to go wobbly and then it would be different. Then she has to relearn how to walk. So, we really didn't know what to expect - [16,F,4,I,M_G]

This quote demonstrates the obvious anxiety brought on by uncertainty regarding the whole BoNT-A procedure. This family assumed a loss of walking ability following injections. It highlights for clinicians how important it is for parents to be given enough information to prepare themselves for the intervention, so that they can best support their child.

In several cases, the reality of the procedure was better than parents imagined. This appeared to be related to how well sedation had worked. As this mother shared, the amnesic properties of the midazolam sedation used prior to administering the injections was a positive experience as her child could not remember the procedure:

So she just had a good time and she says that .. she can't quite piece it together, and we think that's good. [16, F,4, I,M_G]

This contrasted to the experience of another mother who had a very stressful experience with her daughter's procedure:

I thought she wouldn't have a clue what was going on, let alone reaching for me and screaming for me to make them stop hurting her. [60,F,6,11,M_P]

Children's distress during the procedure, despite sedation, understandably results in anxiety for parents together with guilt for 'putting their child through it'.

Uncertainty about how children would respond to the injections on the day was an issue frequently reflected in the data. It further added to parents' anxiety regarding the procedure. It was also more worrying for some parents when the child had a lack of awareness regarding what was about to happen, as one mother of a child with autism reported. She shared her concerns that she was worried that she couldn't prepare him before the injections:

Yes, I was a bit anxious. But more for him than me, because obviously he wasn't very aware of what was going to happen, so it was me as a parent who was more scared and worried for him. But I felt so at ease. [7,M,12,1,M_G]

This quote also highlights the mismatch between expectations about what *could* happen and what *actually* happened during the procedure. In this instance, the mother's recollection of the event was in the end a positive one for both her and her son, as she 'felt so at ease' despite her initial worries and concerns.

11.4.3 BoNT-A -Timing and extent of the impact

Uncertainty regarding the impact of BoNT-A treatment was frequently expressed by parents, both short term and long-term following injections. The data suggested that having not only the correct information, but also knowing enough detail about the variety of different responses to treatment, was empowering for families.

There was a great deal of uncertainty about when the families might see a response following the injections, as these parents noted in relation to their son's first set of injections:

I think the first time we thought he's going to be like jelly, but no, it was nothing like that. That's what I expected, but it was nothing like that, he was absolutely the same as it was the day before
[33,M,4,III,M+F_G].

This family was preparing for the worst but saw no change at all. Conversely, another mother of a four-year-old girl, also having first time injections pointed out that more information would have allowed them to plan for all eventualities:

If you said ... it could kick in at 24 hours, or it could take up to four to six weeks. It would pick up and really you don't notice it, or you might notice it straight away. It's a gentle thing, you know, that's the other thing. It's not this sudden thing where everything goes floppy. I thought she wouldn't be able to walk because this muscle would be floppy and that she'd have to re-organise. It's quite a gentle thing when it kicks in. That would have been really helpful to know.[16,F,4,I,M_G]

Being aware of the facts appeared to enhance the control families had over the procedure as well as improve their degree of 'preparedness' both for their child and their child's wider community, such as school and friends.

In some cases, discussion with other families prior to treatment introduced an element of doubt and uncertainty about whether the treatment would work at all for their child. However, the sharing of other families' experiences was generally considered useful for providing realistic expectations for parents embarking on treatment for the first time. This was highlighted by one mother trying injections for the first time with her 12-year-old son:

I'd spoken to quite a lot of other mums, and some of them said that it's worked with their children, and some of them said that they haven't seen that much change. So, really, I went into it expecting that perhaps not, but for him it's worked massively.

[68.M,12,III,M_M]

It was apparent that speaking to other parents often alleviated anxiety, lowering expectations as to the magnitude of response to expect:

I wasn't worried about it, I just wondered how effective it would be. Because I spoke to so many other people-, and they said, 'mm, not that brilliant'. I mean, you don't know how it's going to be, because all children are different, aren't they? They're all different. For him, I think, I couldn't tell you how much I think it's worked for him ... It's fantastic. [68.M,12,III,M_M]

Families with less access to shared previous experience appeared to have a greater degree of uncertainty and experienced anxiety in putting their child through the 'trial' of treatment. One mother referred to the gravity of the situation, describing it as a journey which ended well:

Yes, it did feel like a really big deal before we did it. We were like, 'We're going to experiment with this. It's going to be good for her. We're not sure.' Really, we were almost less happy to do it, but it was really good. :.... You know, it's all a journey....[16,F,4,I,M_G]

This echoed the feelings of several other parents suggesting BoNT-A was another 'stage' on their journey of navigating interventions for children with CP.

11.5 Engagement- managing uncertainty and anxiety

Although parents alluded to the anxiety and uncertainty they sometimes felt when embarking on their BoNT-A journey, the data revealed a number of elements which

helped to alleviate anxiety and provide more certainty. These appeared to focus on three areas of engagement related to; parents, children and the wider community all underpinned by the provision of information and adequate communication.

Parents shared examples of what was helpful and not so helpful in managing both theirs and their child's uncertainty around the BoNT -A treatment process. Weaving through the data were examples of engagement and rapport building, which suggested good examples of family centred practice when things went well. This was reinforced with good information sharing with parents children, and local community services.

11.5.1 Parental Engagement

Parental involvement and engagement within healthcare settings is recognised to be multifaceted in nature (Goodall and Montgomery, 2014). In practice, communication and engagement opportunities take place weeks before the injection procedure in the out-patient clinic. Baseline assessments occur and the BoNT-A process is explained in order to help families make an informed decision and try and alleviate anxiety and uncertainty. Clinics can provide a less pressured environment for many families than on the ward on the injection day. The data suggested that parents generally appreciated the time taken for pre-injection assessments and the opportunity to discuss their child's care. It was apparent that communication about the treatment process was important to parents as it enabled them to prepare both themselves and their children for what to expect:

it's amazing because, there's lots of time for questions and there's really good assessment. [33,M,4,III,M_G]

Other parents shared they had '*more than enough information*' [66,F,4,III,M_P]

The data showed that providing information appeared to be as relevant for families undergoing repeat injections as for families coming for the first time. A mother whose child was having injections for the first-time said:

To be honest, the information, it meant, as parents, it meant everything was perfect ... because everything was explained, if we had any questions, we felt we could ask them, and no question was too stupid. [10,F,4,II,M_P]

This quote illustrates the importance of building rapport, an essential factor in engagement and making families feel at ease. Positive involvement and communication with the whole team was an experience shared by others, as in the case of a boy coming in for his fifth set of injections whose family highlighted the importance of the team approach both in clinics and on the ward:

Yes, amazing. I knew what was going to happen, whole team spoke to me, told me what to expect and where we would go from here, so I was fully aware. [7,M,12,1,M_G].

Other families referred to a whole team approach highlighting both the professionalism and care during the injection procedure:

The whole procedure itself, the care ... this isn't just one person, there's like a team of five the whole time ... I mean, surrounded by professional care [66,F,4,III,M_P].

However, questions about the injection period also prompted suggestions about how with more information, parents could have prepared their own children better for the procedure. One mother of a child with autism and a more severe motor disability (GMFCS III) shared how her uncertainty about the procedure may have elevated the degree of anxiety her son experienced on injection day. She suggested ways this could have been alleviated:

if you have little handouts for children to look at in the run-up ... parents can just have a look at it so they can see that, actually, on the day, by reminding (them) in the book it said, "you can have the cream on", and then they remember. Because I know on the run-

up ... he kept asking me questions and he was getting himself in a state. And I was trying to reassure him, but kids work with things a lot better when it's visual. [59,M,6,III,M_P]

This quote, amongst others, highlights the challenging role and responsibility parents have managing their child's care. As an expert in her child's management, this mother was aware of the best way to help him, i.e., through the provision of visual information, and with more information this could have been part of the planning process.

Parents also suggested ways to improve communication between families and professionals, emphasizing that communication needs to be a two-way process. One mother, for example, suggested alternative methods of communication could work better due to everybody's lives being 'so busy' (professionals and families alike), she would rather check with her daughter any change in performance in the immediate time after injections:

If you just ask me via e-mail, I think then it would take me five minutes, [my daughter] and I could have a quick chat, rather than saving it for six months. [1,F,5,1,M_G]

The potential problem of 'recalling' the child's response to injections because appointments are often spread over months is highlighted here and also by other parents.

This dynamic approach of communication, enabling parents to "*come to these meetings a bit more prepared*" [1,F,5,1,M_G] referenced a family's desire for 'preparedness' not only for the injection procedure but also for the post injection assessments, reinforcing that parents and children are active partners in their own care.

Many parents demonstrated that they were not only active partners but essential drivers in their child's care, with one parent for example suggesting that they could

prepare for the clinic assessments by recording videos of their child doing activities at home and in the community, reasoning that it would provide a more meaningful picture of their child's progress:

If you say what the things that you want to see are, and then if we video it at different times, because ... there's a lot that you don't see. [16,F,4,I,M_G]

This mother reported the frequent mismatch between what her daughter did in clinic during formal testing, which was more a measure of capacity, and her child's usual performance which she observed in the community. An ability to capture a child's usual performance is something parents are very aware of, and it is highly pertinent both to parents and professionals particularly when planning ongoing treatment. It was apparent that active engagement with the family in terms of how best to assess their child's 'normal state' could help reduce parental uncertainty as to whether professionals had captured an accurate picture of their child's need for, and response to BoNT-A.

Another family identified communication issues regarding letters and pointed out that the language used in reports between the hospital and the local team was often confusing and highlighted how medical jargon can often add to uncertainty and anxiety. They suggested how to improve clarity in the way information is presented to families with a request to ensure accessibility for all:

I don't understand any of it though, that's the thing. When the reports come through, I don't understand ... make it simpler. There are too many big words in it, and I have to look it up ... to see what it says, what you're meaning by it. [3,F,4, I, M_M]

These parents frankly shared the difficulty they had in translating what the professionals were saying about their own child. This quote emphasises the need to communicate in plain English, acknowledging differing levels of literacy as well as medical understanding. Although it is essential to communicate with the referring

local teams, parents are experts in their own child's care and are drivers of the treatment with ultimate responsibility for their child. Engagement must be facilitated by improved clarity of communication.

The 'Busy-ness' of children's lives was also frequently emphasised, "It was manic for appointments" [51, M,5, II, M_G]. A number of parents shared the logistical problems of co-ordinating all of their child's care following BoNT-A injections. Children are scheduled for increased therapy during this time and frequently have orthotics appointments to make new splints. In some cases, this can be overwhelming for families, and parents expressed uncertainty about whether they could fit everything in. The data highlighted the importance of rapport with parents and need for professionals to be sufficiently engaged in order to understand the burdens that are often placed upon families and to see the child in the context of the whole family.

Parents also reflected on the time pressure that everyone is under and emphasized the importance of ensuring that communication channels are robust. This was highlighted by one mother who valued reminders about follow up appointments "with everything else that goes on ... with a disabled child, sometimes you do forget" [10,F,4,II,M_P]

11.5.2 Team around the Children

The data suggested that a child focused, whole team approach was important to parents. Individualised management plans tailored to the needs of the child were considered crucial.

Many families valued the time that professionals spent with their children carrying out physical assessments, before the procedure in outpatient clinic, "*He loves it, he thoroughly enjoys it. He thinks this is the fun appointment*" [51,M,5,II,M_G] as well as during the injection procedure. Children were recognized as being central to the BoNT-A process with parents valuing their child being involved including being transparent and honest about what was going to happen:

I think it's good. Because, you know, you talk to the adults as well, but children are also involved in it, so you don't hide anything from them. Now Y's had it done, I definitely wouldn't say it's anything to be worried about. [59,M,6,III,M_P]

Much of the data highlighted positive engagement between children and professionals during the injection session on the ward. Parents cited examples of good engagement with well prepared, friendly experienced staff. There were frequent references to the wider team:

You just see the experience, the physios, nurses, the way things are, the way it's set up, it's just amazing. [1,F,5,1,M_G]

Other parents talked about being well prepared for injections (both parent and child) and described the feeling of a 'team around the child', as in the case of this mother who described her child's first experience:

All of it, fantastic. More than enough information. The whole procedure itself, the care, ..., I mean, this isn't just one person, there's like a team of five the whole time, whether they're the play therapist or they're the physio ... or anyone, I mean, surrounded by professional care. I feel it was a perfect experience.

[66,F,4,III,M_P]

When it worked well, many parents reported having a positive experience on the ward, with their children not being unduly stressed and 'proudly' talking about the injection experience afterwards with their friends:

I thought everyone was very friendly, she wasn't distressed. She was actually quite looking forward to it ... she enjoyed the whole day ... she had been looking up to it and telling everyone, 'I'm going to have my Botox.' ... she talks about her Botox quite often. Any time any hospital gets mentioned, 'I've been to hospital, I've

had my Botox.’ And it’s a proud ... Yes. Nothing put her off from it, so, and we talked about, ... what was going to happen, about coming back to have it again, and she seems fine. [63,F,5,II,M_M]

There was also an acknowledgement from some parents of the skill of the team in engaging and distracting the child and the positive impact of a play therapist, as the mother of a five-year-old boy explained:

He didn't even know he was having it done. He was waiting for them [injections]... He asked us when he came out. ‘I thought we were having injections’ ... the young girl [play therapist] was talking to him and she had the little laptop thing, and she was asking questions ...And he's totally focused on that because he wants to say the right thing, doesn't he? Because he wants to impress her. And seriously, he never knew nothing ... he was so concentrating on the game, he didn't even flinch. [51,M,5,II,M_G]

Tailoring the distraction specifically to each child’s age, anxiety level and cognitive ability was seen to aid in the preparation of the injection session. Teamwork between the injecting team, play therapist and ward staff appeared to alleviate anxiety for the child and family. Early engagement with children ensures as good an experience as possible. This is particularly important as in many cases children have to return for further injections.

When the experience was a good one it was encouraging to hear how the procedure was rated positively by both parents and children. Tailoring interventions to individual need was important and involved the expertise of the team. This was highlighted in the quote below, when several distraction techniques were used:

I think the thing that we appreciated was the dog therapy, I think it was a small thing, but he really enjoyed it and it just comforted him.... she [the play therapist] let him watch something he wants to watch, so to be fair, he was watching it and having the actual

injection didn't impact him ... he was so focused on watching that, he forgot what was going on at the other end. [33,M,4,III,M_G]

This anxious boy was so distracted that he hadn't been aware that the injections had even taken place. Distraction also appeared to be related to the child's awareness of the injections, and how awake they were. Many parents talked about the impact of sedation on their child's injection experience. A number of families were unsure about 'what to expect' and there was a lot of uncertainty about how their child would react to the sedation and how much their child would 'feel' the injections. Parents reported less stress surrounding the injections when their child experienced what they considered to be an 'optimal' level of sedation, together with positive distraction therapy as provided by the play specialist and wider team:

*When you take her in, ... you're really good with her, when she's in there the play person is really good. We have story time...
[3F,4,1,M_M]*

In the following quote the family referred to a deeper level of sedation together with distraction which worked for their daughter:

Well, they said it has an amnesiac, which I hope it did. So, she just had a good time and she says that, she can't quite piece it together, and we think that's good. The actual process of having the injections was amazing. It couldn't have been more brilliant, and you can see that she's almost not conscious about it's happening [16, F,4, I,M_G]

These positive comments contrasted sharply with parents' feedback regarding distressing scenes when their children were having injections and anxiety levels were high, as in the case of a six-year-old child who had undergone a previous traumatic procedure without sedation.

This quote acknowledges the immense guilt her mother experienced putting her child through it again when the second injection session also did not go well:

She was screaming, looking at us, wide eyes saying, 'Mummy, make them stop. Why are you letting them do this? Mummy, make them stop,' she fought the sedation ... as soon as she came out ... she went to sleep ... I thought she wouldn't have a clue what was going on, let alone reaching for me and screaming for me to make them stop hurting her. And she was dreaming about it afterwards and started waking up in the night as well ... Her anxiety went mad, and she was not having none of it, and I was like I'm never putting her through that again. And I said to her, I'm not putting her through, especially as this time it didn't work.

[60,F,6,II,M_P]

This disturbing quote highlights the extreme parental anxiety which can be associated with an invasive procedure such as Botulinum Toxin injections. Parents are often uncertain about whether they are doing the right thing. In this case the child had a poor response to this set of injections and the family did not see any change and further treatment was not recommended. We hear in this account the traumatic experience that both the child and the parent went through – the mother holding her daughter whilst the injections took place. This experience highlights the potential for having a long-term effect on both the child and the parents, which has continued beyond the injection period.

The above example highlights the importance of giving parents and children the opportunity to voice their concerns when things don't go well. This is essential in order to minimize further distress for the child in the future both on the ward and in the preparation for further procedures.

It was apparent that experiences differed between families however, a difficult experience during the injection procedure didn't necessarily put families off from

trying again. One father recalled the details of the procedure, and highlighted how the injection experience affects everyone, parents and children:

The event, the actual event ... you did it nice and quick and everything else. But, emotionally, I think it was draining for her, it was draining for me and I'm quite a tough guy, so, but it was very draining for me and I think that has been a flashpoint for her. She will know something's happened there. So, yes, I don't want to say, 'Oh, it was terrible.' It wasn't terrible, it was just ... to be honest, really not sure [about] the sedation, what it did, because she still screamed in there ... it's the wait, it's the anticipation, that is not good for her. [70,F,4,III,F_M]

This quote highlights a number of different issues, the intense emotion that parents experience as well as the effect on the child and the impact of waiting for the injections to happen, all leading to heightened anxiety. These experiences can impact on the difficulties parents face when persuading their child to have further injections.

There was much uncertainty from parents regarding how sedated children would be, as well as how much they would remember about the event. This was a point constantly revisited by parents about the anxiety of choosing to put their child through further injections and something that must be acknowledged when preparing children for repeat injections.

11.5.3 Engagement with the community

The data provided information about the challenges parents can encounter when trying to help their child engage with the wider community, following BoNT-A treatment. They were often uncertain about what to do to support their child and appreciated being signposted by the GOSH clinical team to other participation opportunities.

This was highlighted by parents of some of the more able children:

because you took the extra mile, he's done his running, he played his football, and it was fantastic [7,M,12,1,M_G].

You do support because on certain events like obviously when we came post Botox there would be some things I've noticed that [child] will be struggling with, and your colleagues ... have printed off ... local clubs in the area that X could benefit from ... like a CP football group. [1,F,5,1,M_G]

The interviews highlighted some issues about communication between families and their local teams, with parents being concerned that there was not a three-way traffic of communication between themselves, GOSH and local teams:

[GOSH] communicating with my local team perfect, my local team communicating with you is the issue. [10,F,4,II,M_P]

The data suggested that this can often increase anxiety levels and uncertainty about future management of their child if communication is not open and fluid. Following successful treatment with first time injections for her four-year-old daughter, another mother expressed frustration about a perceived lack of involvement with the local team in making a future plan for further treatment. This was expressed in relation to the consultant paediatrician who planned to leave further assessment for a year:

After not expecting it to work and then it working really well... because from our consultant's point of view, "we saw her after eighteen months and now we're not going to see her for another year" [16,F,4,I,M_G]

Uncertainty regarding ongoing management can be a source of anxiety for parents. This mother frustratedly highlights the amount of time and energy they have put into the treatment process.:

The physiotherapist said she might try and put something in, in a few months. So, now it's worked really well and we've had the good result ... and now she's beginning to tighten. Actually, now we've got no plan for her! You invest all this time and energy ...That's it, they need to have a plan! [16,F,4,I,M_G]

This quote highlights a break in the link between treatment from a tertiary service, engagement with the family and a perceived lack of engagement from the local team following injection. As drivers of future treatment, parents want to be part of ongoing planning and preparation. Uncertainty about future plans can be challenging for families as they often lack the control to coordinate input around BoNT-A treatment. They are willing to put their child through this procedure but need to have a plan about what happens next.

11.6 Impact through the ICF lens

Conversations about the impact of BoNT-A injections on children's lives generated data that could be mapped onto all of the ICF domains of Body function and structure (BSF), Activity and Participation. However, most examples given were practical illustrations of how injections had improved activity and participation, as well as impacting on their child's behaviour, endurance, and quality of life issues such as confidence.

11.6.1 Body structure and function-improving endurance

When describing how their children had changed following injections, parents talked in general terms about the ease of 'physical handling', referring to a change in muscle tone and how their child's muscles felt, or how their limbs looked, but rarely about anatomical changes. Descriptions included the child being 'weaker,

(51), legs feeling 'softer' [51], or ankles being 'less tense' [70], with one parent explaining that it was 'like the muscles were switched off for a while' [16], and others describing the muscles being 'actually numbed'. Improvements in 'stretch' and 'flexibility' [33] were identified, with one parent referring to walking being 'really tight' [56] beforehand and 'loosening up quite quickly' after injections.

Usually when parents described physical changes in their child, this was closely related to a general change in activity. As the quotes below highlight, this was the case for families of children with different motor abilities (GMFCS III and GMFCS II respectively) who received injections for the first time:

There was a drastic improvement to what we saw after we had the injections ... there was a change in her physical handling, everything else, she just seemed to be starting to do different things ... there was a difference from that point onwards.

[70,F,4,III,P_M]

We'll see him just doing something small ... like he'd start jumping.

[51,M,5,II,M_G]

The data indicated that families were predominately focused on how much their child could 'do' after treatment and they drew a connection between the physical manifestations, how their child 'felt' after the injections and any change in activities that they observed.

Many parents felt their child had improved endurance, with one mother relating her daughter's improvement post injections relative to her twin sister:

Well, she's not on her tiptoes, like, she doesn't get told to get off her tiptoes as much, she can go [walk] longer now. She doesn't

get pains in her legs. She's pretty active... her twin sister is likely to start moaning about being tired before she will! [37,F,5,I,F_M]

This example highlights how changes at an impairment level, such as not walking on tip toes, resulted in an improvement in the distance her daughter walked. This quote emphasises the importance of environmental and family factors; a child lives within the centre of their family and children shouldn't be considered in isolation. This mother illustrated this perfectly, measuring the improvement in her daughter's endurance by comparing her to her typically developing sister without CP.

Whilst several families acknowledged the role injections had in improving their child's endurance, one family was keen to point out that it was the combination of BoNT-A plus other interventions which allowed their son to improve his motor ability:

His endurance has improved massively. I would say from this time last year to now, amazing that improvement ... He's changing and growing, he's on medication, Botox, physio, so all of these factors, I think, play into it. I think it's almost like the first time he had the Botox, we felt like he was at a plateau, and this just gave him a little bit of a boost. [33,M,4,III,M_G]

A number of parents emphasised the need to put extra work into rehabilitation, describing it as "BoNT-A plus", "it's not just the Botox... You have to do the therapy" [33,M,4,III,M_G] "six weeks' intense physio as well... that makes a big difference" [3,F,4,II,P_M]. In the example below, another mother re-iterated the need to combine injections with other interventions:

It all coincided, so he had his injections, he got his splints, he got his lycra suit and he got his block of physio all at exactly the same time ... everything was just all done to all coincide, so we got the maximum out of the injections. [51, M,5,II,M_G]

This quote also gives an insight into the busy lives of families who have a child with CP, a topic repeatedly discussed in the context of receiving injections, in some cases, this can be overwhelming and described by some parents as “*manic*”. It is important to recognise the external factors and understand the burdens that are often placed on families and their commitment to maximising the benefits of BoNT-A treatment.

11.6.2 Activity and personal factors

11.6.2.1 Improved confidence

When discussing the positive impact of injections parents frequently talked about a change in their child’s confidence after the injections. This manifested socially, physically, and emotionally with improved determination, independence, and interaction with their peers.

Parents described their child’s improved determination to interact with other children and adults and put themselves physically into new spaces:

She wants to do things; she wants to walk. She knows she can't, because she knows exactly what she's got, but she's just got more determination at doing things. [70,F,4,III,P_M]

Parents talked about how, even if they couldn’t necessarily feel a marked change in how the muscles felt, they observed improved confidence associated with improved stability:

I don't feel any difference, but for her, she's more steady. Even when she's on her splints, she's much more steady after her Botox ... Steadier, more confident. Much more competent ... it gives her tons of confidence [66,F,4,III,M_P]

This example of improved confidence post treatment is particularly interesting given that this child was classified clinically as a poor responder by the clinical team.

The improvement in activity and resultant change in participation following injections was brought out in several interviews. Parents described an improved confidence associated with this increased participation, leading to, or resulting from, an increased interaction with their peer groups and the opportunity to make friends, as illustrated in the following quote:

She's more mobile in her walker, which is brilliant, because she can actually run around in the playground with her friends. So, she's getting more confidence to build friendships [66,F,4,III,M_P]

This quote illustrates the strength of emotion when a mother sees a positive change in her child. It's what children do with the improved mobility, 'building friendships', which is so good for the family to see.

Other parents also talked about improved confidence linked to improved activity, and one family was keen to share how their son's swimming ability had improved following injections:

Yes, he wasn't enjoying swimming at all, and it really shook his confidence because his friends were at a different stage to he is, and he found that quite hard. But I think now he feels more able and it's given him a bit of confidence as well. He just goes for it now and tries his best [56,M,9,II,M_P]

The example highlights particularly well the link between physical improvement, self-esteem, enjoyment and participation.

11.6.2.2 Improved independence

Parents talked about their child's increased independence around the home, describing improvements in important activities of daily living such as "stairs were easier"[62] and they were "going up and down the stairs"[51] independently for the first time. The link between confidence and independence is highlighted clearly in the following quote:

She's more confident climbing stairs now, before she wanted someone behind her all the time whereas now she'll do it herself [3,F,4,1,M_M]

Other parents measured success in improved walking and reduced falls:

I think he's more confident now and he's more happy now. He's not on the floor every ten seconds. He can actually stand up and walk [7,M,12,1,M_G]

The quote above from a mother of a twelve-year-old boy pointed out that improved balance brought about an increased confidence affecting his mood. This highlights the complex relationship between physical limitations, in this case frequent falls, and a child's mood and self-esteem.

Improved independence was important to families, with physical improvements such as improved stability meaning a child could be less reliant on their parents to support them, even if they were not fully independent:

First thing I noticed was, where I walk with him and I have to support him underneath usually or hold two hands. And so he can walk just holding one hand to the car and back. And just how much more stable he was and not wobbly. [68.M,12,III,M_M]

Improved ease with everyday activities was also highlighted in another child with a less severe motor disability (GMFCS II):

While the injections were at their strongest ... he was just walking off the kerb, up the kerb, you know, no hesitation, no worry ... he just does it, rather than more thinking about doing it [51,M,5,II,M_G]

This quote from a mother gives an insight into how a change in an everyday activity such as stepping off a kerb, made life easier for her son, resulting in improved confidence.

11.6.3 Participation

11.6.3.1 Function, fun and family- realising potential

During the interviews, parents were keen to share the fun activities that their children participated in such as jumping [51], skipping, swimming [7], gymnastics lessons, and tennis [16]. They talked about their children 'running a lot better', 'running a lot more' and the fact that it was not so 'uncomfortable' for them to run [3]. Parents were understandably animated and proud when describing their child's achievements:

He played his football, and it was fantastic [7,M,12,1,M_G]

Highlighting what children *could do* allowed families to concentrate on the positive and move away from a focus on impairment (limitations of body function and structure), which tended to emphasise what their child *could not do*. This mother illustrated the increased independence that her child with limited motor ability (GMFCS III) had experienced in being able to cycle further:

Definitely I think cycling has even become easier ... initially, with the bike, I mean, we would barely get halfway and then we'd need to push him and stuff, and now, at this point, he's doing, like, three laps. In six minutes each, you see, so that's quite an improvement [33,M,4,III,M_G]

This mother went on to say that they knew that there was more work ahead, but they were extremely happy with their son's progress and most importantly so was he:

Look, he's got, obviously, he's got a way to go, but it's not that, it's, like, trying to get the best out of him, the best that he can be. The best he can be, yes, and I think he's doing amazing, I mean, we're pleased with his progress ... And he feels very pleased ... he does, definitely! [33,M,4,III,M_G]

The quote highlights realistic expectations of change, and links closely with families being instrumental in goal setting and evaluating goals for treatment interventions, and best placed to measure change post injection, themes which will be explored further in section 11.8 when discussing ways of measuring outcome.

Parents' desire for their child to realise their full potential was echoed in many interviews as a driver for treatment as well as a barometer of treatment success, particularly participation at school as this father shared:

At school, she'll stand at the school table ... participating more than she was ... She wants to stand a bit more ... I think in that way it's helped. [70,F,4,III,P_M]

Recognition of change by the wider community was seen as a positive impact of treatment. One mother described increased involvement from her son's school in encouraging participation:

School are pushing him harder, daily mile ... frame-football ... Swimming ... faster, better. [68.M,12,III,M_M]

Parents also shared some of the wider challenges and burdens on the whole family when trying to encourage their child's participation in the wider community, with one mother explaining that finding the right clubs can be a challenge as well as a financial burden:

It's a struggle to get her into the clubs and a lot of money. Because the ballet, she found hard, so yes, we want to get her into street dancing. [3,F,4,1,M_M]

This point highlights the importance of engagement with the family and local community but also illustrates the inequality of access to participation opportunities.

11.7 Managing expectations

Interviews revealed that whilst there were positive impacts as described above in terms of children's activity, parents also shared experiences related to 'adverse' reactions, variation in children's response to treatment and their views on re-treatment. These came together to highlight the importance of helping parents to manage expectations in relation to the post-injection period.

11.7.1 Adverse events /side effects

Adverse events following BoNT-A are well documented and fall into three categories: procedural events (those happening at the time of injection) such as bruising or pain at the injection site, adverse events attributable to BoNT-A injections such as localised weakness, bladder instability and flu like illness and more serious systemic effects such as generalised weakness, dysphagia, and death. The more generic term 'side effects' is often used when advising parents, both terms are however used interchangeably in the clinical setting.

In clinical practice, parents are advised to look out for the common side effects following injections and these are detailed during the consent procedure. In an attempt to move away from an emphasis on clinical questioning by the researcher, adverse events were not specifically asked about during the interviews. However, parents were encouraged to talk about what didn't go so well following their children's injections.

As illustrated in this section, a few parents reported mild and transient effects which lasted up to three weeks. The most severe adverse events reported related to two children who experienced weakness and episodes of bladder instability.

Parents were generally open about the side effects children experienced. This was especially pertinent with families who had received a number of previous injections.

The mother of a five-year-old described how her son was always a bit worse in the first couple of weeks:

Just after, it's like it makes them worse. Because obviously, they seem to become a lot weaker, but then the physio kicks in
[51,M,5,II,M_G]

This mother didn't appear unduly concerned by her son's reaction, instead accepting the weakness as an expected side effect of the treatment, probably because this was then followed by a positive response to injections. Generally, parents reported that the side effects were transient and had cleared by the time they were reviewed in the hospital six weeks later:

There was a little wobble in the first seven to ten days ...after that, she was upstairs, everything. [70,F,4,III,P_M]

The importance of being prepared for any adverse events came through strongly, as highlighted by the parents of a child with limited motor ability who used a frame to walk (GMFCS III) and experienced initial weakness and bladder instability:

We were aware that there was going to be a bit more wobbliness but we would still make her do the same things prior to the Botox, and then just assisted her a bit more, than slowly eased off. So, I think we were quite positive in that respect. Because you have to know things, like the toilet. Yes, it's very, very important.[70,F,4,III,P_M]

The sense of pragmatism that comes across in this quote reflects the experiences of other parents, when describing their child's similar transient bladder issues:

It's worked a bit better this time, quicker and more effectively ... but he kept on needing to go to the toilet quite a lot ... really sudden, he just got to go. [56,M,9,II,M_P].

In the context of managing expectations, these quotes highlight the importance of families being forewarned about potential side effects. By the time the three families quoted above were interviewed, the issues their child had experienced had resolved, and parents appeared unphased, particularly in the context of a positive response to BoNT-A as in the first two quotes.

11.7.2 Variability in response to injections - how long does it last?

Parents were keen to share their experience about how long the effects of the injections lasted:

Every time he's definitely had a good improvement... Yes, a good few months, I'd say ... I think it was after six months and they said his range was still just as good as it was ... the improvement he gained the first couple of times he's maintained [19,M,6,M_M]

Parents talked about a variation in both the timing of when they first observed change following treatment and also how long the effects lasted for their children. This mother illustrated the gradual change some children experience:

I wouldn't say you see any difference overnight, but it's when you all of a sudden, you sort of think back a few weeks and you think 'they couldn't do that' [51,M,5,II,M_G]

A number of families talked about effects being noticed within 'a period of weeks' [70] whilst others reported seeing change up to three months after the injections:

We didn't see it straight away, like I said, it was a good, I would say three months in ... I think following the injections, there wasn't that much of an initial difference, but I think we just persevered with the physio, and I think over the weeks, there was definitely an improvement. Yes, it wasn't immediate. So, it's weird, I don't

know if that's what's supposed to happen, but it was over that chunk of time. [33,M,4,III,M_G]

Whilst the chemical effects of BoNT-A reportedly last for 12-16 weeks, in some cases the functional effects last even longer (Carr et al., 1998). This quote highlights the uncertainty families can experience in relation to how long the injections *should* last. Another family believed that their child's benefits lasted longer than they had expected:

It has lasted for quite a while, yes, because I know the effects only last for six weeks, but I think it does last a lot longer than that. In the long run, yes. [19,M,6,M_M]

Parents talked openly about noticing when the injections had started to wear off, one mother described the change in her daughter as being quite dramatic and related it to a marked physical change:

'Her tripping and her falling is much worse now. There is tightening ... she's been falling' [16,F,4,I,M_G]

Yet when asked, unsurprisingly she explained that her daughter finds it hard to articulate how things felt different:

Obviously that muscle was kind of switched off for a while, and the switching off is a really gradual thing, and that's why it's hard for her to answer that question, because she's actually not that aware, because she has that same outlook, whether it's difficult or easy. [16,F,4,I,M_G]

She describes how, like many young children, her daughter isn't aware that a change in her walking ability may be because of the injections wearing off. In keeping with her young age 'she just gets on with it'.

She talked about the language that her daughter used to explain how things have changed:

She'll say things like, 'Mummy, I'm really wobbly.' That's what we notice. 'I'm really wobbly. I feel shaky.' She won't be as confident with her balance in tasks, but she has the same outlook, whatever. She doesn't have that awareness yet, but we could see the difference when suddenly it kind of went back. [16,F,4,I,M_G]

Other parents talked about observing a 'quick decline' and gave practical examples of walking up and down a kerb after ten months:

he's started to hesitate again ... it wasn't gradual ... it was more sort of, all of a sudden. [51,M,5,II,M_G]

Closely listening to parents' accounts of change are essential to guide the need for further treatment, as in this quote by parents of a child who had injections for the first time:

If I'm honest with you, I don't think it's improving, I do think it's plateaued. But I do think it's assisting her because of the way that she's moving her body and doing some things. [70,F,4,III,P_M]

Parents as experts in their child's care are an essential part of the future management planning, as their child's advocate they are central to the decision making about the need for further injections.

11.7.3 BoNT-A Re-injection

When considering managing family expectations, a separate theme emerged from the data in relation to retreatment options. Some evidence from the literature suggests that children may benefit more from the first injection session with less response on subsequent reinjections due to physiological changes in the muscle (Johnston et al., 2020). The researcher was therefore interested to see if this

aligned with families' own experiences. A variety of experiences were shared regarding the effects of repeated injections.

11.7.3.1 Magnitude of change with retreatment

Decision making regarding retreatment resulted in additional anxiety for some parents. Uncertainty was expressed about the magnitude of response they could expect to see with repeat injections, with one father distinguishing between maintenance and improvement:

So, it's now about seeing if we can jump up to a different level or if it's maintenance. If it's maintenance, then I'm not sure that's the way we need to be, but if we can hopefully just get even a 2% increase, then we're going the right way, aren't we?

[70,F,4,III,P_M]

Whilst this father clearly felt that to put his daughter through more treatment, there had to be more than just 'maintenance' of her current state, small gains (in this case 2%) were perceived to be better than nothing. The hesitancy and uncertainty about doing the 'right thing' for their children was a recurrent theme in the interviews. Families expressed anxiety about parenting a child with cerebral palsy and being unsure about the correct way to deal with their child's changing needs as they grew- consistently citing improved participation in everyday life as a driver for wanting further treatment despite being unsure that the benefits outweighed the disadvantages.

Parents were asked whether they had noticed a difference between injection sessions, and within the data a variety of responses were presented with positive, negative, or uncertain reactions given.

One mother, for example, was extremely positive about her child's second set of injections and described a sustained impact:

I'm really glad we didn't stop after the first. I think that was excellent ... The first one really made a big difference, but then ... I think with the second it was just better, the growth, the more confidence, the learning how to swim, and the injection just all came together. Hard to know what proportion, but it just felt really, like, 'VOOM,' [1,F,5,1,M_G]

Whereas another family did not see any improvement:

It wasn't as effective as the first one, but I do base that on the fact that there was no follow up from physio after her block of treatment, which I think is paramount to get the maximum success ... Second time I don't think we got a lot out of it I don't think she lost as such, but I don't think she gained anything extra [66,F,4,III,D_P]

As highlighted earlier (Section 11.4.3) parents recognize the importance of BoNT-A being part of an extensive rehabilitation package and highlight that for optimal results it should not be used in isolation.

Another mother of a twelve-year-old boy with good motor ability (GMFCS I) described how her child's fourth injection session resulted in positive functional benefits, despite the third set being disappointing:

The first two times he had it done, amazing, fantastic ... which I would score ten out of ten, the third time I didn't see a significant amount of change ... maybe it just got used to it, or I'm not too sure ... so I think you're at a pace because the first time and second time you can see things moving, and then, the third time was less. Maybe he got to the goals and everything by then. But the fourth

time we did something different, I remember when you did the hamstrings, and then we were like, WOW, because you took the extra mile, he's done his running, he played his football, and it was fantastic [7,M,12,1,M_G].

This variation in response between injection sessions makes it difficult to predict whether a child will benefit from subsequent retreatment. This lack of certainty regarding response to repeated injections has implications for managing parental (and child) expectations.

11.7.3.2 Maturation

A further challenge in managing uncertainty for parents is the impact of the child naturally maturing with age, making it very difficult to differentiate between maturation and the benefits of an intervention:

I don't feel that she would be as strong if she hadn't had the Botox, she wouldn't have been able to get as strong, and to be as normal, to be with her peers and doing what they were doing ... I know that, as they get older, they get stronger anyway, but I think that the Botox injections have helped [her] in achieving that a lot more [62,F,10,I,M_G]

This experience was mirrored by other families who had had repeated injections, questioning whether progress was due to treatment or natural development. This added further uncertainty around deciding about retreatment, an issue relevant to many CP interventions and not unique to BoNT-A treatment.

Another family, when asked whether the benefits of injections were reduced each time, were keen to stress that with their daughter, they had seen more functional benefits with each set of injections. Once again, they related this to their daughter's improved confidence and increased determination to participate in a number of activities:

No, there is more response ... When she had her third time it lasted a lot longer than the first and the second time ... See, with her P.E. at school she's doing a lot more, she has a lot more confidence in the P.E. doing the balance beams and things like that, she's a lot more confident. She is trying more. She does outside games now as well, with Game On, which is her football thing [3,F,4,1,M_M].

Again, parents related success following injections closely to the activities their children were doing and the amount of participation they achieved. The responses aligned from several families and appeared to be independent from the number of injection episodes their child had received.

11.7.3.3 Mixed results

In some cases, parents who had observed a negative response the first time had gone on to try further injections just to 'make sure' and had further disappointing results, with no deterioration but also no improvement in stiffness in the muscles:

I actually noticed he was falling over more. I noticed that he fell over more after having it done the first time, and then the second time it just didn't change anything. The stiffness was exactly the same as it was before. [59,M,6,III,M_P]

Parents are extremely sensitive to changes in their child's condition following treatment, they are aware of when things change for the better and for the worse. This quote illustrates the role of parents as experts in their child's care. It emphasises the importance of parental opinion which should be central to planning future treatment options. Parents know their children, and family opinion was closely aligned to clinicians' reports of physiological changes in the muscles.

Parents whose children had undergone multiple injections naturally drew comparisons between them, often moving between describing these as positive and negative. This was highlighted in the case of a family whose child had had a variety

of responses, initially good, a poor response and then no response leaving the mother describing her overall impression as 'neutral':

If you'd asked before, when it was going great ... I would said I loved it, brilliant, and then if you'd asked me the last time I would of said I really don't like it, but we've had the good and the bad, so kind of neutral about it now [10,F,4,II,M_P]

The data suggested that parents were very aware of weighing up the benefits to their child and this family had now decided to discontinue treatment following a poor response. This highlighted again the role of parents as experts in their own child's care, with a responsibility for decision making, actively choosing to discontinue treatment in alignment with the clinical team.

As the case above illustrates, when things are going well parents recognise the change in their children and are often delighted with the intervention. The benefits following injections are often articulated using emotive language such as '*blown away*' [68], '*drastic improvement*' [70], '*a massive difference*' [1], '*fantastic*' [7]. When injections had not been as successful the language was more subdued, negative comments about the impact and how BoNT-A injections adversely affected mobility included '*worse*' [10] a '*struggle*' [59] and '*minimal*' [60].

One mother described her child as '*unlucky*' when describing an experience of over weakening with injections and serial casting, resulting in increased trips and falls which in fact resulted in the child accidentally stabbing her mother with a fork! [37] Another boy had a bad experience with serial casting following injections resulting in an infected heel which stopped him walking for six weeks, but his mother did not blame the injections:

Stiffness afterwards was probably a bit worse, but then I put that down to the fact that he hadn't been on his feet rather than the injections. I don't actually think that was because of the injections.

[59,M,6,III,M_P]

This could suggest a reluctance for parents to blame the intervention that they have put their child through. Within the clinical assessment clinicians need to offer families the opportunity to express disappointment in the treatment, especially when thinking about a future management plan.

The data suggested that there was a large emotional impact on parents when repeat injections didn't result in any positive benefit for their child and several parents talked about blaming themselves. This regret was highlighted by one mother, who also shared the highs of treatment working well with her daughter, and the lows when things did not go as well as the first time:

Seeing your kid's foot or limb go limp after watching it be stiff for so long is a beautiful feeling. But then, when you've got your heart and soul set on that again and then it doesn't, you feel like a really cruddy parent because you've made her go through that and there's no point ... and then it didn't work, so I felt even worse, because we put her through it thinking this is going to benefit her. It isn't about what we feel, it's about what's good for her, and then it didn't benefit her at all. [60,F,6,11,M_P]

This mother's account was particularly poignant as her daughter went on to have orthopaedic surgery during the time of the study. Her voice is a powerful reminder about the pressure parents are under to improve things for their children and the challenges they face.

11.7.3.4 Anxiety of preparing children for retreatment

There was a consistent theme of first-time experiences laying the groundwork for future anxiety or lack of anxiety when a child had to have further injections, this was true for both children and parents alike. Families faced a challenge when submitting their children to further injections when an injection experience had been traumatic, with sedation and distraction therapy not working optimally for their child.

One family who were keen to try further injections articulated the challenges they had faced even getting the child to return to the hospital for a clinic appointment. Following a negative experience, this mother was very distressed about how to tackle bringing her daughter in for further injections:

I don't think anything we do is going to change it, no ... she's set in her ways, she cried last night because she didn't want to come here she said, 'It hurt' I had to convince her that we were only coming here today to talk [70,F,4,III,M_M]

The parental role in decision making and preparation of their child is paramount. Some parents expressed concerns about the future and repeat injections, with several causes cited. One father was concerned about upcoming planned repeat injections as he was anxious about how his four-year-old daughter would react in future sessions now that she knew what the injections felt like:

It's sort of role reversal, because knowing that we're going back into that situation, it's different to not knowing. Not knowing, you're just trying to get through the day and prepare the best you can. But knowing that we're coming back to do that, there's a lot of factors there that need to be taken into consideration for it to be successful again. [70,F,4,III,F_M]

The factors that he referred to were preparing his child as she remembered the injections and became extremely distressed about the previous set. Her stark recollection of the day contrasted with other parents' accounts when their child did not remember the actual injections.

Whilst the family very much acknowledged their parental role in preparing their child for the next set of injections, they shared their concerns at putting her through it again. Her mother voiced her anxiety about their chance of success and sought guidance in improving the experience:

I was more than happy with the preparation going into the injections [last time], not an issue... She's not going to be the same this time... How do I, for lack of a better word, incentivise her coming?' because I really do think she's going to struggle to the extent of, 'I'm not doing it'. [70,F,4,III,M_M]

The data has shown the team around the child is very important and engagement for both the parents and child is paramount for the next injection session. Benefits of injections need to be weighed up with the amount of distress caused by injections. Some parents talked about this having a negative effect on other hospital visits.

11.8 Measuring Outcome- are we measuring what matters to families?

This section focuses on whether standardised clinical tests and questionnaires relate to parents' perceptions of any change occurring following BoNT-A treatment

11.8.1 Capacity vs Performance

In practice, formalised testing takes place during hospital clinic appointments. It comprises of baseline assessments to decide on the best course of treatment and follow-up assessments to evaluate the impact of treatment following injections. There are concerns that assessing children in artificial clinic conditions may only be a measure of 'capacity', i.e., what a child can do when trying their best in standardised conditions and not a reflection of the reality of everyday life (Burgess et al., Holsbeeke et al., 2009). Such concerns were raised by a number of parents including this mother of a high functioning four-year-old who provided insight regarding the functional *capacity* measured in testing:

There's a lot that you don't see. So even though you spend ages doing a really good assessment, but you didn't 'see' the things. They've been trained, and that's really amazing that they do that,

*but it means that the result isn't the real-world
result...[16,F,4,I,M_G]*

Children frequently improve on 'standardised' tests due to repetition and '*they become very good at doing the same task*' [16,F,4,I,M_G]. This mother recommended that clinicians should ask parents to observe their children doing everyday tasks when they don't know they are being watched, rather than just evaluate the impact of injections in a clinic setting:

Just walking that short distance, she can do it very, very beautifully, but...walking into the clinic and walking out on the street, she kept putting this foot in front of that foot. It was going at an angle and she was stumbling over it. [16,F,4,I,M_G].

A measure of a child's true capability and performance is something clinicians try to reproduce in a clinic setting, but realistically it's often challenging to measure everyday performance. Parents acknowledged this, describing assessments as '*quite easy*'. Motor difficulties in CP are varied and can involve reduced endurance which is often harder to evaluate clinically:

*But hers, it's more the long-distance thing that would hurt her, but then I don't know in a room, can you push her? I don't know.
[63,F,5,II,M_M]*

Logistically a test of endurance may be hard in a clinical setting, however, collaborative goal setting can work to improve therapy outcomes effectively and efficiently (Darrah 2011). This is essential if clinicians are to identify meaningful change during standardised testing, as parents advised that clinical teams don't always see '*the real current situation*' [16,F,4,I,M_G]. For the more able children there were some suggestions about how children could be challenged further with cycling and walking longer distances to test endurance, but parents recognised the limitations of the physical space at the hospital.

The variety of motor abilities of children who took part in the study meant that whilst testing for some did not always reflect their true performance, others enjoyed the challenge of individual standardised testing, particularly when they felt they could demonstrate their true performance:

He loves it ... he enjoys all the challenges because it's just him. He isn't really competing with anyone else, so it's all well

[51,M,5,II,M_G]

This mother highlighted the importance of one-to-one assessments for her son, as he would have found it emotionally challenging being measured alongside other children and not been able to demonstrate a true measure of his motor performance:

If you were to mix it up and do group sessions, you wouldn't get half of what you get ... Because he feels, like, someone else is doing it better and he won't try so much. [51,M,5,II,M_G]

The mismatch between capacity and performance is a cause of anxiety for parents, particularly when the issue of re-injection is to be considered:

Her last Botox assessment it was very good, I was actually shocked in the room at how straight she could walk and how well-aligned it was... However, actually, her tripping and her falling is much worse now, there is tightening whereas you didn't see the current situation, the real, current situation [16,F,4,I,M_G]

By observing her daughter's best 'capacity' in clinic, this mother was concerned that her daughter would not be eligible for further injections as clinicians were not seeing her true 'performance'. Once again this highlights the parents' role as experts in their own child's care and the need to acknowledge parents' opinions as well as capture a child's true performance.

11.8.2 Goal setting

The data suggested that parents were keen to set specific, measurable treatment goals for the injection sessions. Collaborative goal setting is essential, but the challenge is to identify areas which may reasonably be expected to improve following BoNT-A treatment. One father explained that they were helped in the process by clinicians explaining the treatment plan and relating how the muscles to be injected would facilitate the attainment of a goal:

So, the goals are great... we get asked what the main problem is.. and then we...set the goals together. Okay, we're going to do the hamstrings because we want to try to improve the sitting posture, improve the heel strike,' 33,M,4,III,M_G]

However, several parents expressed how difficult they found it to set realistic goals for treatment, particularly when it was the first time that their child had injections. This mum expressed concerns that her initial goals may have been too ambitious:

I feel we might have been a little bit too up there ... with the standing [70,F,4,III,M_M]

Yet, the father of the same child disagreed, highlighting the personal nature of goal setting, he was thinking about the long-term picture for his daughter:

I think that we're on target for the goals... I'm not setting goals for our next set of injections, I'm setting goals that I want to achieve.... Long-term goals. [70,F,4,III,F_M]

As confirmed in the literature, some parents expressed difficulty setting goals and found the process 'quite hard' and emotionally challenging too:

I found it very hard to set the goals anyway because at the end of the day, I just want her 100%, and it's hard to actually rate [that]. [63,F,5,II,M_M]

This example highlights that goal setting can be distressing for some parents because it is a reminder of the gap between their child's development and that of a typically developing child. The acknowledgement of this gap has often been the driver for seeking treatment. The same mother went on to explain that talking about goals was a challenge in front of her daughter especially as '*she gets older*'. Goal setting in this parent's mind concentrated on what her child couldn't do rather than what she could do, and she found this a negative experience and worried about how this affected her child's self-esteem:

You know, because she always hears ... you don't even realise she's heard, and you're like, oh okay ... it comes out later... but yes, you're quite mindful to always be positive, but, yes, it's quite hard.

[63,F,5,II,M_M]

The aim is for children to be involved in collaborative goal setting as much as possible, but this can be difficult for very young children. As clinicians we need to be sensitive to this issue and involve children as much as possible, helping parents identify goals which are participation focused and framed in a positive manner (Verkerk et al., 2021)

Another family reiterated this point claiming their goals centred around more general long-term aspirations:

It was just like he leads a normal life without it affecting him, as much as we can really. [56,M,9,II,M_P]

When asked about goals during the interview, parents did not often refer to specific goals set before the injections but tended to express more feelings about their hopes and aspirations for their children.

Some parents, having set goals, doubted the accuracy of evaluating them later and this father went onto say that he found it hard to score the goals:

I think when you're looking at the scales and stuff like that, might as well just throw a dart at a dartboard but it's okay, that's not an issue [70,F,4,III,P_M]

This quote links to the uncertainty highlighted by many parents about the magnitude of response to expect following injections. It also refers to the variability in children's performances, in clinic children demonstrate their best motor ability 'capacity' often described as their '*clinic walk*'. When at home parents can score either 'capability', what a child is able to do at home (at their best), or they can score their 'performance', what they *actually* do every day at home. This all leads to a variety in response making goal evaluation complicated, which depends on the family and also the skill of the professional team in guiding families to select realistic, achievable goals.

11.8.3 Quality of life and Participation

Two questionnaires capturing health-related quality of life (CPQOL) and participation at home, at school and in the wider community (PEM-CY) were introduced specifically for the study. Parents were asked to feedback on their experiences in completing these and reflect on how meaningful they were.

Some families appreciated talking about more holistic factors, regarding their child's care. The introduction of questionnaires such as CPQOL offered an opportunity to open a dialogue with clinicians about emotional wellbeing of children in the study:

I don't think I've ever been asked, until today, how he feels mentally. It's always been quite physical, which is obviously understandable because that's the aim of the thing. But then, to be fair, I think he's only just reached that age where it would start affecting him maybe more, But I think it might be good to just maybe ask, you know, how the child's feeling, because some parents might not bring it up. Because they might not feel like it's relevant [59,M,6,III,M_P]

Other parents shared that completing the questionnaires together offered the opportunity to discuss issues outside the home with their children, as questions were raised about activities at school and in the community.

Although the feedback indicated parents were overall receptive to completing the questionnaires, a number of families reported that they found them too long and didn't find them particularly relevant:

It's difficult, I can't pretend I enjoy it,, In my view, I think it's more, doing the physical stuff with [child], and looking at it, and filming it, and looking back at those films to see the progression.

That, I think, is more important than some of those questions

[62,F,10,I,F_G]

This father described the questionnaires as not being helpful and preferred the other physical tests rating them more important in evaluating change in his very able daughter.

Some families commented on the lack of context to the questionnaires, which whilst chosen as the only validated measures for CP, were not specifically designed for the British population:

I think they're a little dated and ... it doesn't really fit what you're trying to do ... I would look at the structure of them a little more

and refine them. [70,F,4,III,P_M]

This lack of context and cultural relevance (particularly questions regarding family finance) was picked up by another mother:

Yes, some of them can be a bit long-winded.. some of the questions are a bit repetitive as well, yes. and some of it wasn't

really relevant.[19,M,1,M_M]

Several families found them relevant but too long, with one mother giving insight into the increased burden families face:

Look, if anything, and this is being a bit picky, but there was no problem filling those questionnaires in, I think it was really nice to reflect back on it. I just think ... it would be better to have it slightly shorter because it is time-consuming and, you know, you have to really think about it ... you know, you've got to think about the goals, there's quite a bit of writing to do. [33,M,4,III,M_G]

Another mother's account of filling in the questionnaires also highlighted the importance of considering the added burden on the family:

it's something that you have to really, really read through. To be honest with you when I do these questionnaires it's about 25 minutes because some of the questions are loaded one way slightly, so you could do a negative when it should have been a positive and vice versa. Some of them don't follow on extremely well. I think some need to be batched in a certain different way, but I understand why it's done, but I think it's just more a case of when you fill them in, it's not to do it quickly you have to give it a hell of a lot of thought. [66,F,4,III,M_P]

And other families found them confusing:

I struggled with those I find the wording, trying to make sure I write the right answers, they're a little bit, almost, twisted ... I just had to focus a little bit more ... it was just, like, what do they actually mean? [63,F,5,II,M_M]

Parents were also asked about the additional burden and whether it would have been easier to complete the questionnaires online rather than in clinic:

I don't think it made much of a difference, to be honest, no.... .. it was quite easy because I just did it whilst they were seeing X in the appointment anyway. [19,M,1,M_M]

This quote was representative of all the families interviewed, they did not express a strong preference and most families reported they completed them in clinic whilst their child was performing the movement tests over the hour's appointment.

Are we measuring what is important?

Generally parents reported that standardised measures did give an indication of a change in activity and impairment following treatment but they expressed that only the questionnaires (particularly CPQOL) gave parents a chance to reflect on changes in children's self esteem and confidence in their physical abilities.

Parents reported observing change in their child's motor ability when watching them repeat assessments and seeing change over the 12 months. They felt that observing change in a number of different standardised tests provided more comprehensive information about the benefits of treatment rather than measuring change in one area such as an individual muscle following treatment.

11.9 Children's perspective on BoNT-A

The semi-structured interviews with children elicited similar themes about the BoNT-A procedure and sharing of experience about having CP. Children articulated this in many incidences more directly than the parents. Each child chose their own medium to express their feelings about treatment. Using the mosaic approach (Carter and Ford, 2014), children were free to choose any of the art-based materials or playmobil™ figures to play with during the interviews. Children also continued playing with these while their parents were interviewed and were then allowed to take their crafts home.

11.9.1 Drivers for Treatment

Children as young as six years old shared their feelings about living with CP and they were specific about the negative physical signs of CP:

CP It's so not amazing ! Tightness in my muscles is painful.

[59,M,6,III,C_P]

Pain seemed to feature significantly (more so than in parent interviews) and children explained about how weather conditions affected their pain in different ways:

[When it's cold] My legs get really cramped, and my legs start to hurt when I walk. [on a warm day] They're good, but my legs still hurt a teensy bit. [60,F,6,II,C_P]

Children were clear about the reasons for having BoNT-A “*Because I have cerebral palsy and my legs started hurting*” [60,F,6,II,C_P]. They articulated clearly how BoNT-A affected them:

it makes me a lot stronger... I can walk easily with feet flat ... I could walk a lot further ... fall over less [62,F,10,I,C_G]

Other children articulated the benefits of treatment by telling playmobil™ figures how BoNT-A could help:

Charlie is going to have his botox to make him better... more stronger it will make him do stuff that is really cool, like jumping up and down to the sky! [63,F,5,II,C_M]

They were clear when explaining to the cut-out dolls why their ‘friends’ should try BoNT-A claiming it ‘might help her walk’ [3,F,4,II,C_M].

Several children shared their feelings by explaining how they would advise friends who were considering treatment:

Well, it will make your legs even better and it will make them even more like different than they used to be. It will make little things easier. All sorts of things like sports and running...And maybe walking, like upstairs and that, and like balancing maybe
[51,M,5,II,C_G]

Some older children wrote letters to their friends about to embark on treatment:

“Botox (from my experience) ... has given me an amazing chance to be able to swim, run and it has limited my cerebral pasley [cerebral palsy]” [56,M,9,II,C_P]

This quote highlighted (as with some parent interviews), a child’s positive experience in terms of improved participation was not always related to the clinician’s view of outcome. In this case, clinicians had categorised the child’s change post BoNT-A as a ‘poor response’, based solely on the reduction in spasticity seen following treatment. This contrasted sharply with the child’s own perception of improvement following injections.

11.9.2 Keeping up with peers

Some children articulated clearly what having CP stopped them doing and how BoNT-A had helped:

Because I can’t catch up with all my classmates. I wasn’t at the same level as everyone else, but this Botox helped me.
[59,M,6,III,C_P]

Sometimes children highlighted the difference after treatment, giving specific examples as in this quote, explaining how school trips had been made easier, keeping up physically with classmates:

I always used to be right at the back, because I couldn't walk as fast as they did.....but last time we went to Tower of London... we were walking for a whole day [62,F,10,I,C_G]

Although children talked about their peers, they concentrated more on their personal participation, such as playing football, giving specific details how injections had helped them:

Well, first of all, I wasn't kicking as much as I used to. I used to let my left leg do most of the work, but now, as I've had a lot of injections, they're about equal now. [62,F,10,I,C_G]

Children with all levels of motor ability shared their experiences of change after treatment. As this boy shared who walked using a frame:

My feet are a bit flatter ... it's helped with my running ... I play for frame football, every Saturday ... it's easier than when my feet were on tiptoes [68.M,12,III,M_M]

11.9.3 The injection procedure and beyond

Older children talked openly about the feeling of having injections:

*Straight away, [it] felt sore I could feel it in my legs
[68.M,12,III,M_M]*

The physical sensations of injections were remembered regardless of the sedation used:

Yeah, well it just stings, and I just feel like there's juice in my leg, it stings for an hour and I feel like the juice is in my leg. I just feel it when I wobble my leg. [7,M,12,1,C_G]

Younger children described the sensation of injections, as in the case of a four-year-old girl who had injections for the first time and was explaining what injections feel like to the cut-out doll she had made:

Yes....it like feels funny and it might tickle, tickly bad ... I was going to say tickly funny. [3,F,4,II,C_M]

Other children shared what they would tell their classmates if they needed injections:

I would tell them that it doesn't hurt ... You just feel that something goes into your leg really quickly ... Yeah, you don't feel, It feels like, you know the sting when you pluck your hair? It feels like it's just gone in. [1,F,5,1,GC]

Some children shared what they felt like in the first few days following treatment

The next day I just feel like, well, it's all gone, I guess, but the bruise is there, and when I accidentally, well, the worst bit is even if you touch the bruise once at night, [7,M,12,1,C_G]

The physical pain associated with injections was highlighted, as well as the weakness children sometimes experience, particularly in the first few days:

Well my leg's probably weak [on the first day], so I probably rest.
So, if it's weak then I can't put as much pressure on it.
[7,M,12,1,C_G].

*Your whole leg feels very floppy. After a bit of a time. It's only, like, the rest of the night, and then in the morning you're okay.
[1,F,5,1,C_G]*

Weakness in the first few weeks was also mentioned by a number of children and they weighed this against the positive effects:

[It's] good, but also bad ... because, like, sometimes when I have it, I fall over after I have it. [37,F,9,1,C_M]

Not all children were positive about the effects of injections, some children couldn't really see any difference when asked if they notice any change:

Not really, I don't feel it. [1,F,5,1,C_G]

Another six-year-old boy was not happy as injections had made him "run slower" [19] and a four-year-old girl explained what was harder for her after injections:

Like when I play... when I'm kicking [hard to kick] its soft and hard [3,F,4, I, C_M]

This quote highlights how hard it can be for young children to articulate the altered sensations that they experience and confirms how important it is to find a way to hear children's perceptions of treatment.

Nevertheless, as in the parents' interviews, some children shared positive thoughts, which all centred around how an increase in activity and greater participation made them feel:

Awesome ... I feel great ... My teacher said I'm better at P.E because I haven't tiptoed. [7,M,12,1,C_G].

This 12-year-old boy felt physically better and was pleased that this had been noticed by others. Whereas another six-year-old girl highlighted how doing more activities had benefitted her confidence:

[I do] Swimming ... Cubs ... Cross country ... Performing arts ... It made me not shy. [19,M,6,II, C_M]

This was also true for the children who had less motor ability:

Happier...because my feet is much more flat... [Marks out of 10?] I would go for 18. I keep saying 'look at me! Look at me!' to everybody. And there've been sometimes where I've been feeling too vain. [68.M,12,III,C_M]

These quotes resonate with parents' perspectives regarding a change in personal emotional factors in their children following an improvement in activity and increased participation opportunities.

The interviews also highlighted how realistic the children were about what BoNT-A could do for them. This 12-year-old boy didn't want any more injections in his legs and wanted to concentrate on injections to his arm:

I think that now my leg's flat, I know it's still stiff, but since it's flat now it's not as hard as it was when I was tiptoeing. So that's why I want it in my arm now, because sometimes my arm can stick up, and that's why I want my arm to get stronger, and basically, I feel like my leg's like stronger ... and I'm really glad. [7,M,12,1,C_G].

Another ten-year-old girl shared how injections made her feel following her seven treatment cycles and now had decided to stop injections for a while:

It makes me a lot stronger... I can walk easily with feet flat ... I could walk a lot further... fall over less [62,F,10,I,C_G]

She even advised others what would make the effects last longer, when discussing doing more therapy:

Well, I would, even though I don't do it! I would do a mix, maybe like one day, do like, say, five or maybe more exercises, then the

*next day maybe do one, then the day after that do five again, then
the day after that do one again [62,F,10,I,C_G]*

As with the parents' data, interviews with children highlighted how even young children with CP are perfectly placed to contribute towards future management plans and should be encouraged to take a central role in collaborative goal setting.

11.10 Discussion

“Investigating the experiences of BoNT-A treatment- Do standardised clinical and patient reported outcome measures relate to child and parent perceptions of response following BoNT-A treatment?”

Families face many challenges having a child with a lifelong disability such as CP (Palisano et al., 2017, Rosenbaum, 2021b, Shevell et al., 2019). The interviews revealed the huge amount of uncertainty parents have regarding the future of their children with CP. As other researchers have observed, a lot of emotional energy is spent worrying about the future and trying to facilitate how each child can realise their full potential (Majnemer et al., 2012). It is widely recognised that enhanced participation is the ultimate aim for parents from all interventions in CP, secondary to lack of physical harm or pain for their children (Honan et al., 2022). As highlighted in the study, parents are constantly seeking ways to improve lives for their children. Families listed many drivers for BoNT-A treatment, highlighting the multifaceted problems raised as reasons for seeking BoNT-A treatment. The physical manifestations of CP result in activity limitation and participation restriction which can have an impact on self-esteem and confidence resulting in a vicious cycle of lack of participation and lack of inclusion.

What was apparent was the need for parents to do something to help relieve their child's physical problems. They were willing to try something for 'anything', even a minimal amount of change. The theme of 'what have we got to lose?' was ever present in the data. This is very much in keeping with other work on intervention in CP with *doing something* being associated with parents not giving up hope on their

children's ability to progress (Gibson et al., 2012). This however did not mean that parents adopted an 'anything goes' approach. Parents were very aware of whether the injections were still providing benefit for their child. They constantly weighed up the pros and cons of BoNT-A once they had commenced treatment. As highlighted in the work of others Lorin and Forsberg (2016), parents were aware that the role of BoNT-A was one component of a successful intervention programme and acknowledged the importance of rehabilitation in addition to BoNT-A.

The belief that parents will continue wanting injections long after the benefits have passed in the absence of anything else was not upheld in this data. Parents were very aware when it was time to stop. They were philosophical in their approach to further injection cycles in the absence of obvious benefit for their children. They also had a pragmatic response to expected side effects following injections and even in the face of what could be considered significant side effects of excessive weakness were in fact 'neutral' in their opinion of BoNT-A. Having tried it they were happy to move on if they could not see the benefit for their child.

Although some parents expressed initial reservations about using BoNT-A, the safety of the drug did not emerge in the data as a significant issue. Many people were familiar with its use in the general population for cosmetic reasons 'it's everywhere' and did not perceive BoNT-A treatment to be an overly risky procedure. Parents were more concerned about the actual procedure of multiple injections and how painful the experience would be for their child. This is consistent with the work of Lorin and Forsberg (2016), who also found the same issue in their interviews with 15 parents whose children had undergone BoNT-A, describing the procedure as 'troublesome'. It is interesting that the children's data did not reflect undue distress regarding the injection process, although they did acknowledge the unpleasantness of the procedure. This could also reflect the amnesic properties of the midazolam sedation, which meant that many of the children could not remember the procedure.

Uncertainty about what to do for the best with their child post-injection focused mainly on not knowing the scale of change to expect afterwards. This was particularly pertinent for children having injections for the first time and was linked to a paucity of information about possible outcomes. Discussing the effects of repeated injections revealed that the results were variable, good, bad and neutral. However, two main issues were highlighted: uncertainty about whether to put the children through the experience again and whether it was worth it for the amount of change that parents had observed.

Uncertainty about the effects of BoNT-A focused on two issues to do with timing of response: when families should usually expect to see a change and how long the effects would last. As described by others in the field, a sufficient level of information is key to alleviating uncertainty about what would happen following injections (Lorin and Forsberg, 2016). Sharing different families' experiences about how long it takes for the injections to take effect from other children's experiences would obviously assist parents in 'planning' both for the rehabilitation and also 'preparing' their child, school and family life about what could possibly happen. Also continuing to warn families that things could be more difficult as they may be '*weaker*' in the initial period would help with preparing families for BoNT-A treatment.

Parents were able to set clear goals for BoNT-A treatment and expressed these in terms of the activities that they wished their children to participate in. Success was measured in terms of improved level of participation rather than change in impairment level for many parents and children. Individualised goal setting was appreciated by many parents, focusing on their child's specific needs. However, not all families found it easy to set goals and some parents found it distressing. In these cases, identifying activities that their children wished to do but couldn't do was often a reminder for parents of the gap between their child and a typically developing child. This focus on the difference in physical ability is hardly surprising as historically rehabilitation for children with CP has followed a biomedical model (Rosenbaum, 2020). Traditional therapy has often been criticised for trying to strive

for 'normal' in the way activities are done, instead of embracing the child's different ways of doing things. The focus on doing activities in a 'normal' way can hinder children's progress and can sacrifice opportunities for participation and inclusion on what has been described as an 'altar of normality' (Rosenbaum and Gorter, 2012). Individualised goal setting should allow children and their families to choose targets that are meaningful for them and embrace what they would like to improve and not focus on what they cannot do (Angeli et al., 2019).

The data suggested that a perceived beneficial outcome following repeated injections was associated with goal attainment in areas of activity and participation. This appeared to be closely aligned to realistic goal setting by families, which in many cases reflected moderate expectations of change following treatment. Successful outcome following BoNT-A was acknowledged by many to involve timely access to optimal rehabilitation.

In exploring the experience of families following BoNT-A treatment within this study, it appeared that the standardised clinical and patient reported outcome measures used did relate to families' perceptions of response following BoNT-A treatment. However, parents evaluation of response centred more on changes in activity, participation and quality of life benefits, rather than changes in impairment. Whilst these areas were reflected in the outcome measures used within this study, as highlighted in Chapter 2, few studies to date have evaluated change within all domains of the ICF.

Parental perception of response generally aligned with clinicians' perceptions of response up to six months following BoNT-A treatment. However, there were exceptions, and in both instances [56,66] whilst response had been rated poor by clinicians, parents reported improvements in activity, participation, and an improved confidence for their children. This once again highlighted that success for most families was measured in terms of activity and participation and was not only focused on aspects of spasticity and impairment.

This has important implications for clinical practice. Whilst the parental drivers for BoNT-A treatment may include increased spasticity, the spasticity impairment is judged by families in terms of how much it interferes with children's functional activity or limits their participation. If clinicians are to evaluate the true benefits of BoNT-A treatment, assessment outcomes need to look beyond the measurement of impairment and include the factors that are most important to children and families, including those which focus on changes in activity and participation. Clinicians should evaluate the value and contribution of BoNT-A treatment in the achievement of functional and participation goals.

Damiano et al. (2021), highlighted this point in a recent WHO working party evaluating the efficacy of interventions in CP:

“If an intervention fails to enhance the quality of life, activity or participation for that child or family either in the short or longer term, is it justifiable?”

In order to answer this question outcomes in all of these domains need to be evaluated.

11.11 Strengths and Limitations

The researcher, whilst known to some of the families, had not been involved in any of the children's injection sessions. It was hoped that this would allow families to talk freely about their BoNT-A experience, with someone who was aware of the intervention procedure at GOSH but was not directly involved. It was recognised that the dual roles of the researcher as clinician and interviewer could have introduced an element of bias or skew to the data as there might have been reluctance on the part of parents to say anything negative. However, the familiarity of the interviewer with the process appeared to facilitate parents sharing of many aspects of their BoNT-A experience, both positive and negative. Parents were very

open about the anxiety and uncertainty they faced not only regarding BoNT-A treatment but also about having a child with CP. This permitted further insight into the reasons why families may choose an intervention such as BoNT-A.

Due to their young age, understandably, children involved in the qualitative component of the study preferred to have their parents present during the interviews and vice versa. This may have affected the unrestricted feedback particularly from parents, as they may not have wanted to share negative feedback about BoNT-A treatment. This did not however appear to be the case as parents were very open about their feelings.

The presence of a parent also meant that in some cases children relied on their parents to answer for them. However, this was also very helpful as parents were able to facilitate the sharing of experiences, particularly for shy and younger children, encouraging them to talk to the researcher. This also helped when choosing craft activities to encourage conversations about children's experiences of injections.

Conducting the interviews at the hospital was more convenient for families. However, practically this did mean that interviews often took place after a long clinic appointment and some children were tired. In these cases, the researcher ensured that children had a chance to play and provided a snack and a drink to allow the children some 'down time' before the interviews. This also provided an opportunity for children to play with the materials before talking to the researcher.

Fitting in with children's appointments did introduce an increased time element for both the researcher and the families. The need for increased flexibility around the time of the interviews limited the number of interviews that the researcher could do, as one interview would often require a two-hour slot. Children may have been more relaxed at home and more forthcoming about their experiences, if interviewed in familiar home settings. Nevertheless, children appeared keen to participate in the interviews and were enthusiastic about playing with the materials provided. In many cases the children did not want to leave the interview setting.

Whilst some children could remember the injection experience, the use of midazolam sedation, with its amnesic properties was often successful in minimizing the unpleasantness of the injection procedure. The researcher asked children directly about their memory of the injection day but if a child did not remember any details the conversation moved on to the next question and the child was not prompted further. This was thought to be important as many children return for retreatment and repeated questioning about the unpleasantness of the injection session could be detrimental to future episodes of care.

Valuable information was gathered from the children's interviews, allowing an insight into the child's experience of treatment. However, if more time had been available, interviews could have taken place over a number of sessions and may have provided further deeper understanding of children's experience of BoNT-A.

The results are from families from one centre and therefore may be limited in their generalizability. Although qualitative research does not generally claim generalization of the findings to a larger population, it does aim to facilitate transferability of the findings (Peplow and Carpenter, 2013). As this study was an interpretative design the aim was to create understanding that could be of practical importance in the clinical area.

Seven main points emerged for improving clinical practice

- Acknowledging a parent's expertise about the best time for treatment can help minimise anxiety and stress for families.
- Recognising parents as experts in their own child's care, aware of the best way to help their child understand the BoNT-A procedure. Providing information about the procedure in advance helps parents prepare their own child, in a manner that is appropriate both for their age and their cognitive ability
- Providing families with sufficiently detailed information about what could happen following BoNT-A treatment. Allowing them, to prepare themselves

for the intervention, so that they can best support their child and others involved in their care (such as teachers and extended family).

- A recognition of the mismatch between formal testing in clinic, which reflects a child's *capacity*, in comparison to their usual *performance* in the community. Families are in a position to provide realistic information about a child's *capability* and *performance* in daily life, reflecting meaningful change post BoNT-A.
- Improving clarity in the way information is presented in order to improve accessibility for all family groups. The language used in reports can be confusing, use of medical jargon can add to uncertainty and anxiety experienced by families.
- Parents acknowledge the contribution of BoNT-A as one part of an extensive rehabilitation package and are willing to commit to this. However, they requested support in optimizing the effects of BoNT-A in order to achieve activity and participation goals.
- Uncertainty regarding the next plan for ongoing management can be a source of anxiety for parents. A lack of communication between parents, the hospital delivering the intervention and local teams providing rehabilitation results in increased anxiety for families.

Efforts were made to include children with differing response to BoNT-A in order to encompass a range of experiences, the sample size of 18 was not small in qualitative terms and it could be claimed that there was an acceptable element of 'information power' (Malterud et al., 2016). The interviews were performed by the researcher, who was familiar with the procedure through her work as a physiotherapist. In an attempt to limit bias in the analysis and reporting of the qualitative data a second researcher (KO) was also used to examine the data. Including the contribution of a second reviewer of the data, who was independent to the service, provided another perspective and enhanced the trustworthiness of the results.

11.12 Future research

There is a need to hear more about the child's experience, particularly about the child's perception of the usefulness of BoNT-A treatment in assisting them *or* hindering them to achieve functional activity and participation goals. There is a paucity of research surrounding the lived experience of families following interventions, particularly the voice of the child. This study makes a contribution to addressing this gap in the literature, but further research is required including children of all GMFCS levels with differing cognitive abilities and of different ages receiving BoNT-A treatment.

Chapter 12 Integration and triangulation of Phase I and Phase II findings

This research utilised a concurrent mixed methods design, with the qualitative data of Phase II of the study embedded within the larger primary quantitative data of Phase I. The focus of this chapter is to bring together the findings from the two phases of data collection with the aim of understanding the multidimensional experience of BoNT-A treatment for CYPwCP and the implications of these findings for clinical practice.

As highlighted in the systematic review in Chapter 2, few studies to date have evaluated change in all domains of the ICF. Of those that did evaluate change throughout the domains of the ICF, the majority did not compare the findings to published MCIDs, resulting in uncertainty regarding the clinical significance of the findings. Throughout this research, change scores within the ICF outcomes have been compared to the available published MCIDs. This permitted the evaluation of outcome in terms of clinical significance to children and families in addition to statistically significant change observed following BoNT-a treatment.

This research used a simultaneous design with both qualitative and quantitative data collected concurrently and analysed independently (Heyvaert et al., 2013). Although the quantitative data from Phase I were dominant, Phase II qualitative data enriched the findings and enabled exploration of families' experience of treatment. This included identifying whether what matters to families was identified in the existing outcome measures. Phase II data were analysed for themes related to changes in the ICF domains and these were used to clarify the effectiveness of BoNT-A in ambulant CYPwCP.

Using mixed methods in this study permitted access to the different aspects of the phenomena of interest, evaluating the benefits of BoNT-A treatment for ambulant CYPwCP, which as other researchers have highlighted could not have been accessed by one method alone (Creswell and Clark, 2017, Morse and Niehaus, 2009, Wu et al., 2019). It can be difficult to capture the essence of experience of both CYPwCP

and their families using only research methods that strive for reproducibility and generalizability, such as systematic measurement of quantitative data. The integration of the data from Phases I and II allowed the recognition of any divergences that emerged by comparing qualitative 'experience' and quantitative 'effect' data following BoNT-A treatment. As a result of identifying change throughout all domains of the ICF, this study was able to evaluate the benefits of BoNT-A treatment throughout a number of areas of a child's life, which are considered meaningful to families and CYPwCP. This is in support of WHO guidelines which has recommended that any intervention targeted at improving body structure and function should be evaluated in terms of improvement in activity, participation and quality of life outcomes (Damiano et al., 2021).

This mixed methods study evaluated objective change in ICF outcomes over a 12-month period following BoNT-A injections. The main findings from the two phases of the study have been summarised in Table 12-1. The 'fit' of data integration refers to coherence of the quantitative and qualitative findings (Fetters et al., 2013). Although the majority of data from Phase I was corroborated by families' experience of BoNT-A treatment, the areas where the data from families' experiences diverged from the quantitative results have been highlighted in red in the table. The following sections will explore the integration of these findings (12.1), together with the implications for clinical practice (12.4).

ICF	Outcome measure	Timing of Clinically significant improvement in Phase I Outcomes*	Qualitative findings Phase II
BSF	Pain	6 weeks & 6 months	Less pain on walking and at night Reduced stiffness, softer, more flexible Walking up and down kerbs
	Spasticity	6 weeks (Gastrocnemius and Hamstring muscles) 6 & 12 months (Hamstring muscles)	
	Selectivity of movement	6 weeks, 6 months & 12 months	
Quality of movement	Alignment	6 weeks, 6 months & 12 months	Improved ease of movement Less tired More fluid movement patterns, less effortful X: parents reported less trips and falls following BoNT-A earlier than 12 months
	Dissociated Movement		
	Weight Shift	6 & 12 months	
	Co-ordination	6 & 12 months	
	Stability	Only at 12 months	
Activity	GMFM-66	6 weeks, 6 months & 12 months	Running, jumping Improved mobility in the classroom and in the community X: parents described children walked further, walked longer, kept up with peers, improved endurance earlier than 12 months
	TUG	6 & 12 months	
	1MFWT	Only at 12 months	
Goal attainment	COPM-Performance	6 weeks & 6 months	Parents were able to set realistic goals, aware when effects of injections had worn off & when to discontinue treatment
	COPM- Satisfaction	6 weeks, 6 months & 12 months	
Participation: HRQOL	CPQOL Feelings about Function Participation and Physical Health	6 weeks-12 months	Improved self esteem confidence happiness joining with peers
Participation: PEM-CY Frequency (F) and Involvement in activities (I)	Home [H] School [S] Community [C]	[H]F/I: 6 weeks, 6 months & 12 months [S]F: 6 months I: 6 weeks, 6 months & 12 months [C]F: 6 weeks, 6 months & 12 months [C]I: No Significant change	Setting the table School mile, playground X parents talked of increased involvement in community activities following BoNT-A such as football, scouts, cycling, judo

Table 12-1 Synthesis of quantitative phase I data with qualitative phase II data

X Divergence of Phase II data from Phase I data [*following adjustment for clinical confounders]

12.1 Synthesis and implications

Body structure and Function Outcomes

In agreement with the published literature, this study found that spasticity was significantly reduced following BoNT-A injections (Blumetti et al., 2019, Delgado et al., 2016b). We did, however, observe a difference in the length of response between the two main muscle groups injected, hamstrings and gastrocnemius. Whilst both muscles showed a short term reduction in spasticity at 6 weeks, only hamstrings showed a continued significant reduction in spasticity throughout the 12 months. The more global measure of 'technical response' within the most injected muscles was in keeping with the literature and showed a gradual return of increased spasticity between 6 and 12 months post injection (Fattal-Valevski et al., 2008, Kanovsky et al., 2009, Multani et al., 2019a). Within the Phase II data, parents described a reduction in spasticity in terms of a change in 'stiffness' lasting for variable durations, and an ease in performing passive stretches and improved splint tolerance, which were individual to each child and treatment episode. Some parents described a sudden increase in spasticity once the effects of BoNT-A had worn off: *"We could see the difference when suddenly it kind of went back", "it wasn't gradual ... it was more ... all of a sudden"*.

A small but significant improvement in muscle selectivity was seen, which was maintained throughout the 12 months of the study. Parents described the consequences of this in terms of improved function such as stepping up and down kerbs, utilising the improved muscle selectivity. There was also convergence of the data regarding a short term reduction in pain which lasted for up to six months which was described by parents and also objectively shown by reduced pain scores.

The introduction of the QFM, the novel outcome measure used in this study, allowed the standardised objective assessment of a change in movement quality for the first time following BoNT-A treatment. Quality of movement was found to be significantly improved following BONT-A injections. However, although an improvement in alignment scores was seen at the initial assessment at 6 weeks

following treatment, clinically significant changes in other QFM attributes such as dissociated movement, co-ordination and weight shift took longer to appear. Most parents interviewed described a generalised improvement in movement quality, such as 'ease' of movement and 'fluidity' of performing activities in the first weeks following treatment, whereas others corroborated the QFM findings and described an increasing improvement in movement quality that was most marked three months after treatment. It is of note that stability, as measured by QFM, was only found to be clinically significantly improved at 12 months post injection. This was in contrast to parents' descriptions of less trips and falls following treatment, which may reflect the multifaceted nature of stability, including changes in co-ordination and weight shift.

Activity outcome measures were improved in the study following BoNT-A injections, this was reflected in families' accounts of change in the amount of activities that children did. Parents and children described a variety of functional activities that the children were able to do better following treatment, emphasising that optimising performance is an ultimate goal in cerebral palsy (Halma et al., 2020). Whilst quantitative data demonstrated an improvement in gross motor function throughout the 12 months, and an improvement in functional balance and gait (TUG), parents also observed an improvement in distance walked which had not been reflected in a clinically significant improvement in gait as measured by 1MFWT. This confirms the findings of other research in this area, which suggests that standardised gait tests such as 1MFWT may not be sensitive enough to pick up change following an intervention such as BoNT-A (Love et al., 2010b). The measurement of endurance was also highlighted as an area not picked up in standardised testing, with additional concerns that although capacity is evaluated in standardised testing, a child's true performance is rarely seen in the clinic setting.

Goal attainment was demonstrated by significant improvement in COPM goal scores over the 12 months. Average COPM performance scores, although improved at all time points were only found to exceed the MCID at 6 weeks and 12 months (approaching clinical significance at 6 months). COPM Satisfaction scores with goal

performance were significantly improved across the 12 months. This was in keeping with parental reports, as families were aware of the effects of BoNT-A wearing off and increased stiffness, nevertheless, many families described ongoing improvement from baseline.

It is of note that although evaluation of response to BoNT-A was closely aligned between clinicians and parents in the majority of cases (~90%), some families also described an improvement in activity, endurance, confidence and self-esteem when clinicians' evaluation of response to BoNT-A treatment (which had been based solely on a reduction in spasticity), had been poor. This emphasises the importance of evaluating activity, participation and Patient Reported Outcomes (PROMs) following treatment in the assessment of treatment benefits. Including PROMs can provide more contextually relevant information regarding children's 'functioning' ability (Holsbeeke et al., 2009). They can also address the issue of measuring capability (what a child *can* do in their current environment) and performance (what they *actually do* in the context of where they live, go to school etc.) as realistically evaluated by PROM's versus measuring capacity (best performance) with standardised outcome measures administered in artificial clinical settings (Fattal-Valevski et al., 2008, Halma et al., 2020).

It would appear from the results of this study that BoNT-A enables CYPwCP to achieve activity and participation goals following treatment and once achieved, these activities seem to be maintained, despite the fact that stiffness may have returned. These findings are in keeping with the work of others in the field who have suggested that BoNT-A has a long term effect on gross motor function in CYPwCP even though the effect on muscle tone is short lived (Fattal-Valevski et al., 2008, Wright et al., 2008).

This study highlighted that the number of previous injection episodes did not appear to be significantly associated with outcome. This was in contrast to earlier studies that showed the first two injection cycles were more likely to result in improved spasticity and gross motor function (Kahraman et al., 2016, Papavasiliou

et al., 2006). Previous injection history within this study was not shown to be a significant predictor for outcome in any of the ICF domains in Phase I data. This was corroborated by Phase II data, where a number of families who had received multiple injection episodes reported a continued positive response which appeared to be unrelated to the number of previous injections. Although it was acknowledged that children having repeat injections (≥ 3) were a smaller, self-selecting group, whose children had continued to show benefit. Nevertheless, parents with children having repeat injections for the second time also described positive changes following BoNT-A, although some parents did describe the magnitude of response to be less marked than the first time.

Age was also not found to be a significant predictor for outcome within this study. Whilst it is recognised that younger children are more likely to have more dynamic contractures than older children, the evidence within this study suggests that when clinical indications for BoNT-A were present, older children were just as likely to have a positive outcome as younger children. Older children demonstrated a significantly greater improvement in QFM attributes and activity outcomes such as 1MFWT and GMFM-66 (after adjusting for other clinical confounders). This was highlighted by the positive reports from children and parents in Phase II, with children who were 12 years old reporting continued benefits. These findings support the work of Strobl et al. (2015) who suggested that clinical indication for treatment of a dynamic contracture in the injected muscle was more important than age (or previous injection history).

The original vision of the ICF was one of a dynamic system of interconnected parts, with the principal purpose being a reminder to focus on what CYPwCP *can* do. This was supported by the findings in Phase II of the study, when parents and children highlighted what activities the children could do better following BoNT-A treatment, identifying personal factors such as confidence and self-esteem as well as functional drivers for treatment.

The approach of evaluating how well interventions optimise function in CYPwCP is in keeping with current views of the practical use of the ICF for family centred practice. Rosenbaum (2021b) and others (Damiano et al., 2021) have suggested that where interventions start (i.e. where interventions are targeted) may be much less important than identifying the broader functional goals that interventions are hoping to change (Figure 12-1).

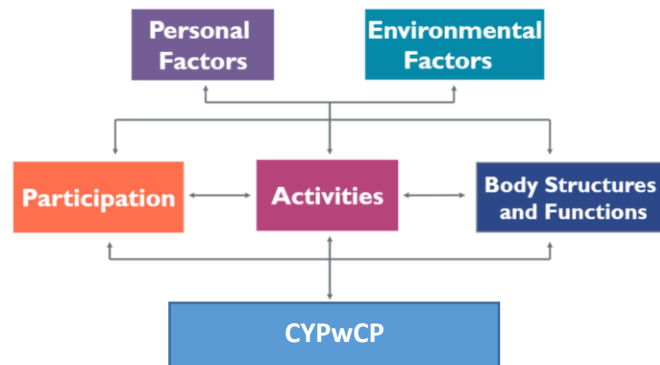


Figure 12-1 Modified ICF adapted from CanChild (Rosenbaum and Gorter, 2012)

As highlighted in Phase II, the main driver for BoNT-A intervention came from a parent’s desire to improve their child’s participation in everyday activities, at home, in school and in the wider community. Children ‘keeping up’, and ‘interacting’ with peers was important to families. The data from Phase I demonstrated an improvement in HRQoL following BoNT-A, as measured by CPQOL in the domains of function and participation following injections, which was consistent with parental reports of improved self-esteem and confidence.

In contrast, participation as measured by PEM-CY (which was not CYPwCP specific), did not show a significant improvement in involvement in community activities. These findings did not align with parental reports of improved involvement in community activities such as swimming, football and judo. This may reflect a lack of sensitivity in generic tools to evaluate change in participation. Change scores were of small magnitude and difficult to interpret in the absence of MCIDs. These findings were in keeping with other researchers who have used PEM-CY who also found it

difficult to determine whether the change in participation scores were clinically meaningful (Gibson et al., 2018, Reedman et al., 2019).

There were limitations in the use of this measure, as PEM-CY may not have adequately captured the parameters most likely to change following BoNT-A treatment, particularly given the small number of questions about physical activities. It is recognised that participation of CYPwCP, like that of typically developing children can be greatly influenced by individual and family preferences (Shimmell et al., 2013). These in turn, can be influenced by factors such as age, level of disability and in some cases gender (Shikako-Thomas et al., 2008). Participation can therefore be difficult to compare directly between individuals or to typically developing children using standardised tests (Sakzewski et al., 2007). This may explain the divergence of parents' experience of improved participation from the PEM-CY data.

12.2 Summary

The mixed method approach within this study enabled the integration of the experiences of children and parents with standardised testing of outcome following BoNT-A treatment, throughout all domains of the ICF. It highlighted the drivers for treatment and gave insight into the factors that families considered important. The results of this study support the approach that interventions should be driven by what matters most to families, 'promoting functioning' (Figure 12-2).

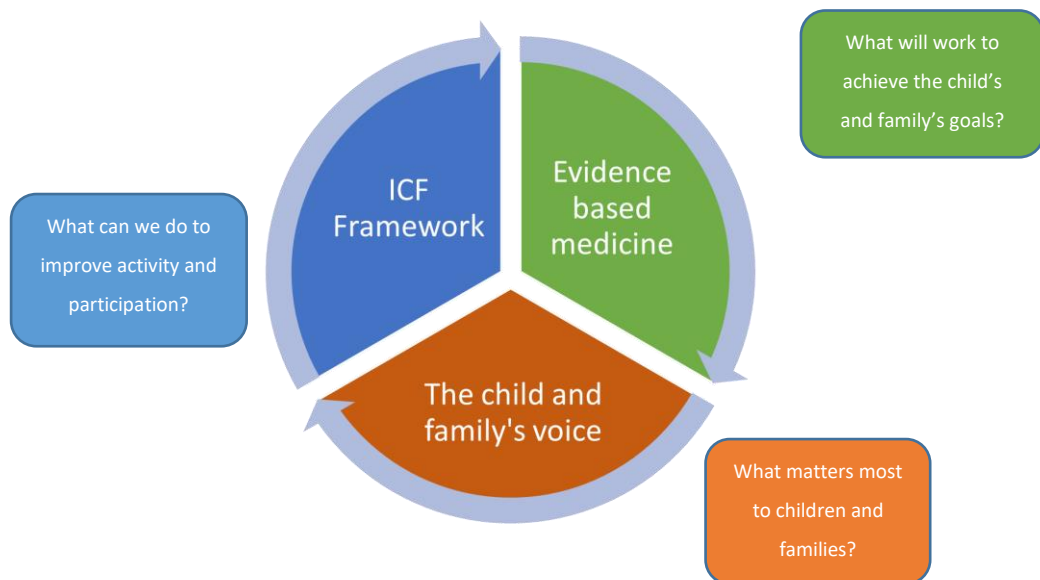


Figure 12-2 A modified biopsychosocial approach to functioning (adapted from (Kraus de Camargo et al., 2019))

Understanding the concepts of capacity (what a child can do with formal testing), capability (what a child can do in their daily environment) and performance (what a child usually does) are important for CYPwCP (Halma et al., 2020, Holsbeeke et al., 2009). Interventions such as BoNT-A may provide an opportunity to minimise the gap between the two and maximise performance.

Within this study the novel inclusion of a standardised measure of movement quality (QFM) provided further information regarding the changes observed following BoNT-A. The results of the QFM confirmed the changes in movement

quality observed by families following treatment, which had not previously been evaluated by other standardised outcome measures. The variation in response within different QoM attributes within this study could have implications for clinical practice. These findings showed a delay in clinically significant improvement in four out of the five QFM attributes until after the initial 6-week assessment period and may provide direction for targeted training following treatment. This could be in terms of the content of rehabilitation programmes (targeting the different quality attributes) and the length of time the period of rehabilitation should last (beyond 6 weeks) in order to potentiate the effects of treatment.

Nevertheless, whilst the benefits of QFM as a research tool have been highlighted, its' usefulness as a clinical tool, particularly in its current format, with significant administration and scoring time remain to be seen. The QFM has been shown to be responsive in evaluating change in movement quality following BoNT-A treatment, however in its current form it is difficult to use in clinical practice. Further work is planned with the test developers combining the comprehensive data set of this study of 239 separate QFM assessments with the developers' existing data set, in an attempt to streamline the scoring of the QFM attributes. This could enable the development of a shorter form of a standardised QoM assessment, possibly using 'item sets' which would require a reduced number of GMFM items to be evaluated. This would facilitate its use in clinical practice to evaluate a change in movement quality following interventions in CYPwCP.

Within this study, the majority of children (62.5%) received a single injection episode over twelve months. Those children requiring re-injection within the study had these almost 10 months following their first injection episode¹¹. These findings support the work of other researchers who have recommended extending re-injection intervals beyond six months and have advocated re-injection intervals of 12 months (Franki et al., 2020, Hastings-Ison et al., 2016). The timing of re-injection following assessment of outcome within all ICF domains within this study is pertinent, particularly when this is considered in the light of emerging evidence

¹¹ Mean time to re-injection 41.3 weeks \pm 4 weeks

which has shown inhibited muscle growth with repeated injections within 12 months (De Beukelaer et al., 2022, Schless et al., 2018).

The experience within this study shows that evaluation of outcome based only at the level of spasticity could result in shorter re-injection intervals if activity, participation and HRQoL are not also assessed. It supports a body of literature which suggests that when evaluating BoNT-A use in CYPwCP, clinicians should move beyond assessing outcome only at the level of impairment with a resultant overemphasis on a change in spasticity scores (as measured by MAS and MTS), so that meaningful outcome can also be evaluated in areas that are important to children and families.

12.3 Strengths and Limitations

As highlighted by the systematic review in Chapter 2, this research is one of the few studies to evaluate longitudinal change following BoNT-A in all domains of the ICF over a 12-month period, using both standardised clinical and patient reported outcome measures. This was the first study to evaluate change in QoM following BoNT-A using a validated outcome measure (QFM), and the only research study to compare all ICF outcomes to published MCIDs.

Whilst the lack of a control group can be considered a limitation of this study, as BoNT-A treatment is considered best practice care for focal hypertonia management for CYPwCP, there were practical and ethical concerns regarding the inclusion of a 'no treatment' control group. The use of a longitudinal study design permitted each child to act as their own control and the use of multilevel regression modelling allowed for the adjustment of clinical confounders. Using MCIDs to compare change beyond that expected without treatment also gave strength to the results of this study. The results from this study suggest focused, targeted BoNT-A treatment to the right child can show benefits in activity and participation domains which can persist longer than the reported short-term reduction of spasticity.

As this was a pragmatic clinical study, there were a variety of different treatment options available (with regards to combinations of muscles injected, as well as the content of therapy delivered following treatment). However, this can also be considered an advantage as the results of this study represent true clinical practice. Therefore, although the research is from a single site, with reference to clinical practice at a specialist children's hospital, the pragmatic nature of the study could make it more generalisable to other centres, particularly within the UK.

The novel use of the QFM as a standardised outcome tool to evaluate movement quality provided useful information regarding a change in QoM following BoNT-A. This detail of change in movement quality following treatment has not been previously reported in the literature and served to supplement the evidence regarding a change in capacity following BoNT-A treatment. However, more importantly it may highlight a change in both capability and performance not usually evaluated by standardised tests. The lengthy administration and scoring time do however limit its' use in routine clinical practice in the current form. Information generated about the correlation between attributes from this large data set could assist in the development of a more streamlined data set and modifying the scoring criteria would make the measure more feasible for use in clinical practice.

12.4 What this study adds to clinical practice

This study has successfully shown that the efficacy of BoNT-A treatment can be evaluated throughout the domains of the ICF in order to assist with clinical decision making, involving both children and their families.

The objective measurement of hypertonia is a well recognised clinical challenge. Whilst more sophisticated instrumented approaches could have been used to measure spasticity, the Modified Tardieu Scale R1 component successfully measured change in dynamic spasticity. The findings were mirrored in the changes observed in MAS for the most frequently injected muscles, gastrocnemius and hamstrings. Although both measures appeared to validate each other, the MTS

provided a more objective measure of spasticity and was able to incorporate information regarding spasticity (R1) in addition to information regarding the non-neural component (R2).

The more global 'Technical Response' introduced within this study endeavoured to evaluate the complexity of clinical practice by assessing change relative to published SEMs for each muscle group injected. This provided a categorisation of response for the main muscle groups identifying 'responders', 'non responders' and those cases that had 'deteriorated'. Work is underway to operationalise this system within DRIVE (Great Ormond Street Hospital's Data Research, Innovation and Virtual Environments Unit), which focuses on data collection to improve clinical care and patient experience. This will allow longitudinal data to be collected for children following repeated injection episodes and outcomes can be compared between the different ICF domains.

The SMC test successfully measured change in muscle selectivity post injection, however in the absence of published MCIDs the magnitude of clinically meaningful change was difficult to assess. The multilevel regression analyses revealed that muscle selectivity was significantly associated with higher GMFCS level (GMFCS I and II) and muscle groups injected (distal versus proximal muscle groups). Muscle strength was not measured in this study but its inclusion in further research could provide useful information following treatment, particularly in the light of emerging science in the area of microscopic and macroscopic change in the muscle regarding more long term atrophy beyond 6 months following BoNT-A.

Within this study, a change in functional balance was successfully evaluated using the TUG and supplemented the findings of other activity measures, particularly with regards to the timing of response (after 6-weeks). Nevertheless, in keeping with the latest Cochrane review (Blumetti et al., 2019), BoNT-A did not appear to significantly improve gait parameters and gait capacity as determined by the timed walk test used in this study (1MFWT). However, parents interviewed in Phase II suggested that improved endurance rather than speed was a driver for BoNT-A

treatment. Future studies could consider incorporating a PROM assessing endurance such as the Early Activity Scale for Endurance (EASE) (Fiss et al., 2019) or the Gait Outcomes Assessment List (GOAL), (Thomason et al., 2018) to capture this phenomena.

The GMFM-66 was effective as a measure of functional activity and was able to discriminate between GMFCS Levels. Magnitudes of change were consistent with earlier BoNT-A studies (Choi et al., 2019, Valentine et al., 2020b). The introduction of the QFM was successful in assessing the impact of reduced spasticity following BoNT-A on quality attributes such as alignment, co-ordination and stability. The QFM was found to be responsive to change and provided additional information regarding the timing of change following BoNT-A over a 12-month period. Clinical practice has changed to incorporate recording the GMFM so that movement quality can be assessed routinely.

The COPM successfully evaluated goal attainment following BoNT-A treatment and the results showed a small but clinically significant improvement in goal attainment. The inclusion of both measures, Performance (COPM-P) and Satisfaction with performance (COPM-S), permitted the evaluation of change that was meaningful to children and families. Evaluating change in individual goals provided more meaningful information about goal attainment than using averaged scores following BoNT-A. Goal attainment outcome was once again categorised in terms of 'responders,' 'non-responders' and 'deteriorated' for the study and has been operationalised within clinical practice in order to evaluate longitudinal change over a number of injection episodes. Goals have also been separated into activity and participation domains in order to provide further depth of evaluation of response following BoNT-A.

PROMs are important in evaluating change following interventions. Within this study the CPQOL questionnaire was able to demonstrate an improvement in HRQoL regarding participation and feelings about function and pain. Due to the young age of children in this study, a proxy reporting measure was used as recommended by

the test developers. However, it is imperative that whenever possible the child's voice should be heard. Children as young as 4 are now encouraged within the service at GOSH to complete their own questionnaires (with the help of an adult) and these now supplement parental questionnaires to assist in planning future treatment.

The PEM-CY was chosen for this study as it is the only validated measure to evaluate participation in terms of frequency and involvement in activities in the home, school *and* community setting. However, the PEM-CY is a more complex questionnaire and a number of parents reported difficulty in completing the measure. A number of countries have developed their own version of the PEM-CY enhancing the cultural relevancy of the measure (Krieger et al., 2020, Longo et al., 2019, Srinivasan et al., 2021). Modifications of this type could improve the use of PEM-CY within the UK.

Both PROMs would also benefit from the development of MCIDs in order to enhance the clinical relevance of change scores of these measures. The results of this study will enhance the knowledge base involving the use of these measures. As this was a longitudinal study with three collection time points following BoNT-A treatment, there is a significant amount of data available. The researcher has established collaborations with international users and the results of this study will assist in the development of MCIDs.

The selection of children for re-treatment with BoNT-A, as previously highlighted by others, appears to be a complex multifaceted phenomenon and should not be based on one outcome measure alone (Heinen et al., 2010, Love et al., 2010b, Multani et al., 2019a, NICE, 2012). Whilst increased dynamic tone is undoubtedly an important factor in using BoNT-A, within this study a return of dynamic spasticity was not always associated with re-injection. Whilst it is tempting to think of a re-injection algorithm purely in terms of a return of dynamic tone, the results from this study suggest that improvements in functional activity, movement quality and participation continue for longer than the reduction in spasticity. Therefore

treatment should be considered in terms of goal achievement and evaluating the sustained effects resulting from BoNT-A treatment and not only the isolated assessment of the return of dynamic spasticity.

Longer re-injection intervals (in the majority of cases over 12 months) were supported by the finding of this study. This was based on the assessment of outcome within all ICF domains, both in the short term (6 weeks) following BoNT-A and also later in the medium term (6 months) and long term (12 months) post injection period when retention of benefits could be evaluated. This permitted the evaluation of change in areas that were considered meaningful to children and families. These findings support national guidelines which recommend assessment of outcome beyond the short term in order to assess meaningful change following treatment (NICE, 2012).

12.5 Recommendations for future research

The main areas for consideration for future research to emerge from The Toxin study were:

1. The development of MCIDs for PROMs evaluating HRQoL (CPQOL) and Participation (PEM-CY), in order to evaluate clinical significance of change in these measures following interventions for CYPwCP.
2. The development and validation of item sets to shorten the QFM test and improve efficiency of administration of the QFM in order to standardise quality of movement assessment in clinical practice.
3. The development of an agreed core set of clinical outcome measures within each ICF domain in order to evaluate the efficacy of BoNT-A. This would permit evaluation of the benefits of BoNT-A treatment over a larger number of participants, involving a number of different healthcare settings.
4. Longitudinal studies investigating a number of injection episodes using a defined core data set. Adequately powered studies will permit multilevel regression analysis of a series of outcome measures and provide information regarding the long-term effect of BoNT-A.

5. Integration of quantitative and qualitative data following BoNT-A treatment with emerging research regarding the microscopic and macroscopic changes in muscles morphology following injections. This will further assist with risk-benefit analyses regarding the benefits of treatment for ambulant CYPwCP.

Clinical research ... next steps

1. Recognising the importance of co-intervention

Evaluation of an extended rehabilitation period beyond the initial short-term reduction in spasticity following BoNT-A treatment, in order to assess long term outcomes throughout ICF domains

2. Improved transition for adolescents into Adult BoNT-A services

Exploration and introduction of clinical outcome measures used in adult services in order to facilitate transition for adolescents into Adult BoNT-A services- consideration of a health passport encompassing all domains of the ICF beyond body structure and function.

12.6 Conclusion

The findings from this study suggest that judicious, targeted use of BoNT-A does have a place in improving activity and participation for CYPwCP which can be maintained up to 12 months following treatment. As with all interventions in CP, outcomes should be evaluated in terms of their success in 'improving functioning', which was one of the main drivers from families for treatment.

Results from this single site study were intended to represent the first stage in identifying predictors to BoNT-A treatment in order to better inform clinical practice and assist decisions that families and clinicians make about using BoNT-A. In order to extrapolate findings to a larger population, multicentre longitudinal prospective studies with standardised primary outcome measures are required to provide sufficient power for multivariate analysis.

Chapter 13 References

- ADE-HALL, R. & MOORE, P. 2000. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd.
- AKAIKE, H. 1979. A Bayesian extension of the minimum AIC procedure of autoregressive model fitting. *Biometrika*, 66, 237-242.
- ALBANESE, A. 2011. Terminology for preparations of botulinum neurotoxins: what a difference a name makes. *Jama*, 305, 89-90.
- ALBAVERA-HERNANDEZ, C., RODRIGUEZ, J. M. & IDROVO, A. J. 2009. Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials. *Clin Rehabil*, 23, 394-407.
- ALEXANDER, C., ELLIOTT, C., VALENTINE, J., STANNAGE, K., BEAR, N., DONNELLY, C. J., SHIPMAN, P. & REID, S. 2018. Muscle volume alterations after first botulinum neurotoxin A treatment in children with cerebral palsy: a 6-month prospective cohort study. *Developmental Medicine & Child Neurology*, 60, 1165-1171.
- ALHUSAINI, A. A., CROSBIE, J., SHEPHERD, R. B., DEAN, C. M. & SCHEINBERG, A. 2011. No change in calf muscle passive stiffness after botulinum toxin injection in children with cerebral palsy. *Developmental Medicine & Child Neurology*, 53, 553-8.
- ALHUSAINI, A. A., DEAN, C. M., CROSBIE, J., SHEPHERD, R. B. & LEWIS, J. 2010. Evaluation of spasticity in children with cerebral palsy using Ashworth and Tardieu Scales compared with laboratory measures. *J Child Neurol*, 25, 1242-7.
- ANABY, D., LAW, M., COSTER, W., BEDELL, G., KHETANI, M., AVERY, L. & TEPLICKY, R. 2014. The mediating role of the environment in explaining participation of children and youth with and without disabilities across home, school, and community. *Arch Phys Med Rehabil*, 95, 908-17.
- ANABY, D. R., LAW, M., FELDMAN, D., MAJNEMER, A. & AVERY, L. 2018. The effectiveness of the Pathways and Resources for Engagement and Participation (PREP) intervention: improving participation of adolescents with physical disabilities. *Dev Med Child Neurol*, 60, 513-519.
- ANGELI, J. M., HARPSTER, K., HUIJS, L., SEID, M., SHEEHAN, A. & SCHWAB, S. M. 2019. Patient-Centered Goal Setting in Developmental Therapy: Discordance between Documented Goals and Caregiver-Perceived Goals. *Pediatr Qual Saf*, 4, e199.
- ANNETTE, M. 2006. Assessment tools for cerebral palsy: new directions. *Future Neurology*, 1, 755-763.
- AOKI, K. R. & GUYER, B. 2001. Botulinum toxin type A and other botulinum toxin serotypes: a comparative review of biochemical and pharmacological actions. *Eur J Neurol*, 8 Suppl 5, 21-9.
- AOKI, K. R., RANOUX, D. & WISSEL, J. 2006. Using translational medicine to understand clinical differences between botulinum toxin formulations. *Eur J Neurol*, 13 Suppl 4, 10-9.
- ASHWORTH, M., GUERRA, D. & KORDOWICZ, M. 2019. Individualised or Standardised Outcome Measures: A Co-habitation? *Administration and Policy in Mental Health and Mental Health Services Research*, 46, 425-428.
- AUTTI-RAMO, I., LARSEN, T. A., PELTONEN, J., KALLIO, P., NOPOLA-HEMMI, J., SILTANEN, K., PALTTO, M., JANTTI, S., TORNIKOSKI, P. & JAAKKOLA, R. 1997. The use of botulinum toxin treatment in children with movement disorders. *European Journal of Neurology*, 4, S23-S26.
- BAKER, R., JASINSKI, M., MACIAG-TYMECKA, I., MICHALOWSKA-MROZEK, J., BONIKOWSKI, M., CARR, L., MACLEAN, J., LIN, J., LYNCH, B., THEOLOGIS, T., WENDORFF, J., EUNSON, P. & COSGROVE, A. 2002. Botulinum toxin treatment of spasticity in

- diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study. *Developmental Medicine & Child Neurology*, 44, 666-675.
- BAKHEIT, A. M. 2010. The use of botulinum toxin for the treatment of muscle spasticity in the first 2 years of life. *International Journal of Rehabilitation Research*, 33, 104-108.
- BALGAYEVA, M., BULEKBAYEVA, S. & DARIBAYEV, Z. 2018. Influence of combined use of botulinum therapy and robotic kinesiotherapy on indicators of general motor function in children with cerebral palsy. *Toxicon*, 156 (Supplement 1), S6.
- BAR-ON, L., AERTBELIËN, E., WAMBACQ, H., SEVERIJNS, D., LAMBRECHT, K., DAN, B., HUENAERTS, C., BRUYNINCKX, H., JANSSENS, L., VAN GESTEL, L., JASPERS, E., MOLENAERS, G. & DESLOOVERE, K. 2013. A clinical measurement to quantify spasticity in children with cerebral palsy by integration of multidimensional signals. *Gait Posture*, 38, 141-7.
- BARBER, L., HASTINGS-ISON, T., BAKER, R., GRAHAM, H. K., BARRETT, R. & LICHTWARK, G. 2014. The effects of botulinum toxin type-A injection frequency on muscle growth in young children with spastic cerebral palsy. *Developmental Medicine and Child Neurology*, 56, 34-35.
- BARBER, L., HASTINGS-ISON, T., BAKER, R., KERR GRAHAM, H., BARRETT, R. & LICHTWARK, G. 2013. The effects of botulinum toxin injection frequency on calf muscle growth in young children with spastic cerebral palsy: a 12-month prospective study. *Journal of children's orthopaedics*, 7, 425-433.
- BARRETT, R. S. & LICHTWARK, G. A. 2010. Gross muscle morphology and structure in spastic cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology*, 52, 794-804.
- BAX, M., GOLDSTEIN, M., ROSENBAUM, P., LEVITON, A., PANETH, N., DAN, B., JACOBSSON, B. & DAMIANO, D. 2005. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol*, 47, 571-6.
- BELL, K. J., OUNPUU, S., DELUCA, P. A. & ROMNESS, M. J. 2002. Natural progression of gait in children with cerebral palsy. *J Pediatr Orthop*, 22, 677-82.
- BJORNSON, K., HAYS, R., GRAUBERT, C., PRICE, R., WON, F., MCLAUGHLIN, J. & COHEN, M. 2007. Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics*, 120, 49-58.
- BLAND, J. M. & ALTMAN, D. G. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1, 307-10.
- BLIESE P 2016. multilevel: Multilevel Functions.
- BLUMETTI, F. C., BELLOTI, J. C., TAMAOKI, M. J. S. & PINTO, J. A. 2019. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. *Cochrane Database of Systematic Reviews*.
- BOHANNON, R. W. & SMITH, M. B. 1987. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*, 67.
- BOWLING, A. 2014. *Research methods in health: investigating health and health services*, Maidenhead,GB, Open University Press,.
- BOYCE, W., GOWLAND, C., ROSENBAUM, P., LANE, M., PLEWS, N., GOLDSMITH, C., RUSSELL, D., WRIGHT, F., POTTER, S. & HARDING, D. 1995. The Gross Motor Performance Measure: Validity and Responsiveness of a Measure of Quality of Movement. *Physical therapy*, 75, 603-13.
- BOYCE, W. F., GOWLAND, C., ROSENBAUM, P. L., LANE, M., PLEWS, N., GOLDSMITH, C., RUSSELL, D. J., WRIGHT, V. & ZDROBOV, S. 1991. Measuring quality of movement in cerebral palsy: a review of instruments. *Phys Ther*, 71, 813-9.
- BOYD, R. & GRAHAM, H. K. 2007. Objective measurement of clinical findings in the use of Botulinum Toxin type A for the management of children with cerebral palsy. *European Journal of Neurology*, 6, s23-s35.

- BOYD, R. N. & GRAHAM, H. K. 1999. Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *European Journal of Neurology*, 6, S23-S35.
- BOYD, R. N. & HAYS, R. M. 2001. Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review. *European Journal of Neurology*, 8, 1-20.
- BOYD, R. N., PLIATSIOS, V., STARR, R., WOLFE, R. & GRAHAM, H. K. 2000. Biomechanical transformation of the gastroc-soleus muscle with botulinum toxin A in children with cerebral palsy. *Developmental Medicine & Child Neurology*, 42, 32-41.
- BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3, 77-101.
- BRAUN, V. & CLARKE, V. 2013. *Successful qualitative research: A practical guide for beginners*, sage.
- BRAUN, V. & CLARKE, V. 2019. Reflecting on reflexive thematic analysis. *Qualitative research in sport, exercise and health*, 11, 589-597.
- BRAUN, V. & CLARKE, V. 2021a. One size fits all? What counts as quality practice in (reflexive) thematic analysis? *Qualitative Research in Psychology*, 18, 328-352.
- BRAUN, V. & CLARKE, V. 2021b. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. *Qualitative Research in Sport, Exercise and Health*, 13, 201-216.
- BREWER, K., POLLOCK, N. & WRIGHT, F. V. 2014. Addressing the challenges of collaborative goal setting with children and their families. *Phys Occup Ther Pediatr*, 34, 138-52.
- BRIN, M. F. 1997. Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity. Spasticity Study Group. *Muscle Nerve Suppl*, 6, S208-20.
- BRUTON, A., CONWAY, J. H. & HOLGATE, S. T. 2000. Reliability: What Is It, and How Is It Measured? *Physiotherapy*, , 86, 94-99.
- BURGESS, A., REEDMAN, S., CHATFIELD, M. D., WARE, R. S., SAKZEWSKI, L. & BOYD, R. N. 2021. Development of gross motor capacity and mobility performance in children with cerebral palsy: a longitudinal study. *Developmental Medicine & Child Neurology*, n/a.
- BYRNE, D. 2021. A worked example of Braun and Clarke's approach to reflexive thematic analysis. *Quality & Quantity*.
- CAGLAR OKUR, S., UGUR, M. & SENEL, K. 2018. Effects of Botulinum Toxin A Injection on Ambulation Capacity in Patients with Cerebral Palsy. *Developmental Neurorehabilitation*.
- CANS, C., GUILLEM, P., ARNAUD, C., BAILLE, F., CHALMERS, J., MCMANUS, V., CUSSEN, G., PARKES, J., DOLK, H., HAGBERG, B., HAGBERG, G., JARVIS, S., COLVER, A., JOHNSON, A., SURMAN, G., KRAGELOH-MANN, I., MICHAELIS, R., PLATT, M., PHAROAH, P., TOPP, M., UDALL, P., TORRIOLI, M., MICELI, M., WICHERS, M. & SCPE 2002. Prevalence and characteristics of children with cerebral palsy in Europe. *Developmental medicine and child neurology*, 44, 633-640.
- CAO, L. & MORLEY, J. E. 2016. Sarcopenia Is Recognized as an Independent Condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. *Journal of the American Medical Directors Association*, 17, 675-677.
- CARDOSO, E. S., RODRIGUES, B. M., BARROSO, M., MENEZES, C. J., LUCENA, R. S., NORA, D. B. & MELO, A. 2006. Botulinum toxin type A for the treatment of the spastic equinus foot in cerebral palsy. *Pediatr Neurol*, 34, 106-9.
- CAREY, H., MARTIN, K., COMBS-MILLER, S. & HEATHCOCK, J. C. 2016. Reliability and Responsiveness of the Timed Up and Go Test in Children With Cerebral Palsy. *Pediatric Physical Therapy*, 28, 401-408.

- CARR, L. J. 2009. The expanding role of botulinum toxin type A injections in the management of children with cerebral palsy. *Developmental Medicine & Child Neurology*, 51, 687-8.
- CARR, L. J., COSGROVE, A. P., GRINGRAS, P. & NEVILLE, B. G. 1998. Position paper on the use of botulinum toxin in cerebral palsy. UK Botulinum Toxin and Cerebral Palsy Working Party. *Archives of Disease in Childhood*, 79, 271-3.
- CARTER, B. & FORD, K. 2014. How arts-based approaches can put the fun into child-focused research. *Nurs Child Young People*, 26, 9.
- CARTER, S. & HENDERSON, L. 2005. Approaches to Qualitative Data Collection in Social Science. *Handbook of health research methods: Investigation, measurement and analysis*. Maidenhead, UK: Open University Press.
- CHALÉAT-VALAYER, E., PARRATTE, B., COLIN, C., DENIS, A., OUDIN, S., BÉRARD, C., BERNARD, J. C., BOURG, V., DELEPLANQUE, B., DULIEU, I., EVRARD, P., FILIPETTI, P., FLURIN, V., GALLIEN, P., HÉRON-LONG, B., HODGKINSON, I., HUSSON, I., JAISSON-HOT, I., MAUPAS, E., MEURIN, F., MONNIER, G., PÉRENNOU, D., PIALOUX, B., QUENTIN, V., MOREAU, M. S., SCHNEIDER, M., YELNIK, A. & MARQUE, P. 2011. A French observational study of botulinum toxin use in the management of children with cerebral palsy: BOTULOSCOPE. *European Journal of Paediatric Neurology*, 15, 439-448.
- CHAMBERS, C. T. & CRAIG, K. D. 1998. An intrusive impact of anchors in children's faces pain scales. *Pain*, 78, 27-37.
- CHANDRA, S., AFSHARIPOUR, B., RYMER, W. Z. & SURESH, N. L. 2020. Precise quantification of the time course of voluntary activation capacity following Botulinum toxin injections in the biceps brachii muscles of chronic stroke survivors. *Journal of NeuroEngineering and Rehabilitation*, 17, 102.
- CHEN, S., WOLF, S. L., ZHANG, Q., THOMPSON, P. A. & WINSTEIN, C. J. 2012. Minimal detectable change of the actual amount of use test and the motor activity log: the EXCITE Trial. *Neurorehabilitation and neural repair*, 26, 507-514.
- CHIEN, C.-W., RODGER, S., COPLEY, J. & SKORKA, K. 2014. Comparative Content Review of Children's Participation Measures Using the International Classification of Functioning, Disability and Health; Children and Youth. *Archives of Physical Medicine and Rehabilitation*, 95, 141-152.
- CHOI, J. Y., KIM, S. K. & PARK, E. S. 2019. The Effect of Botulinum Toxin Injections on Gross Motor Function for Lower Limb Spasticity in Children with Cerebral Palsy. *Toxins (Basel)*, 11.
- CLARK, A. & MOSS, P. 2011. *Listening To Young Children: The Mosaic Approach (2nd ed.)*, London, National Children's Bureau
- CLARKE, N., STEPHENS, J., PULGAR, S., BAINS, S., MARCHESE, D. & TILTON, A. 2016. A review of the health-related quality of life in pediatric patients with cerebral palsy and associated spasticity. *Annals of Neurology*, 80, S371.
- COHEN, J. 2013. *Statistical power analysis for the behavioral sciences*, Academic press.
- CORRY, I. S., COSGROVE, A. P., DUFFY, C. M., MCNEILL, S., TAYLOR, T. C. & GRAHAM, H. K. 1998. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. *Journal of Pediatric Orthopedics*, 18, 304-11.
- COSGROVE, A. P., CORRY, I. S. & GRAHAM, H. K. 1994. Botulinum toxin in the management of the lower limb in cerebral palsy. *Developmental Medicine & Child Neurology*, 36, 386-96.
- COSGROVE, A. P. & GRAHAM, H. K. 1994. BOTULINUM TOXIN-A PREVENTS THE DEVELOPMENT OF CONTRACTURES IN THE HEREDITARY SPASTIC MOUSE. *Developmental Medicine and Child Neurology*, 36, 379-385.

- COSTER, W., BEDELL, G., LAW, M., KHETANI, M. A., TEPLICKY, R., LILJENQUIST, K., GLEASON, K. & KAO, Y. C. 2011. Psychometric evaluation of the Participation and Environment Measure for Children and Youth. *Dev Med Child Neurol*, 53, 1030-7.
- CRESWELL, J. & PLANO CLARK, V. 2011. *Designing and conducting mixed methods research*, California, USA, Sage Publications.
- CRESWELL, J. W. & CLARK, V. L. P. 2017. *Designing and conducting mixed methods research*, Sage publications.
- CRESWELL, J. W. & CRESWELL, J. W. 2013. *Qualitative inquiry & research design : choosing among five approaches*.
- CROWNER, B. E. & RACETTE, B. A. 2008. Prospective study examining remote effects of botulinum toxin a in children with cerebral palsy. *Pediatric Neurology*, 39, 253-8.
- CROWNER, B. E., TORRES-RUSSOTTO, D., CARTER, A. R. & RACETTE, B. A. 2010. Systemic weakness after therapeutic injections of botulinum toxin a: a case series and review of the literature. *Clinical Neuropharmacology*, 33, 243-7.
- CUSICK, A., MCINTYRE, S., NOVAK, I., LANNIN, N. & LOWE, K. 2006. A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. *Pediatr Rehabil*, 9, 149-57.
- DABROWSKI, E., BONIKOWSKI, M., GORMLEY, M., GRANDOULIER, A., PICAUT, P., SNYDER, D. & DELGADO, M. 2017. Efficacy and safety of abobotulinumtoxin a in children with dynamic equinus foot deformity previously treated with botulinum toxins. *Developmental medicine and child neurology*, 59, 30-31.
- DAI, A. I. & DEMIRYUREK, A. T. 2017. Serial Casting as an Adjunct to Botulinum Toxin Type A Treatment in Children With Cerebral Palsy and Spastic Paraparesis With Scissoring of the Lower Extremities. *Journal of Child Neurology*, 32, 671-675.
- DAMIANO, D. L. 2014. Meaningfulness of mean group results for determining the optimal motor rehabilitation program for an individual child with cerebral palsy. *Developmental medicine and child neurology*, 56, 1141-1146.
- DAMIANO, D. L., GILGANNON, M. D. & ABEL, M. F. 2005. Responsiveness and Uniqueness of the Pediatric Outcomes Data Collection Instrument Compared to the Gross Motor Function Measure for Measuring Orthopaedic and Neurosurgical Outcomes in Cerebral Palsy. *Journal of Pediatric Orthopaedics*, 25.
- DAMIANO, D. L., LONGO, E., CAROLINA DE CAMPOS, A., FORSSBERG, H. & RAUCH, A. 2021. Systematic Review of Clinical Guidelines Related to Care of Individuals With Cerebral Palsy as Part of the World Health Organization Efforts to Develop a Global Package of Interventions for Rehabilitation. *Arch Phys Med Rehabil*, 102, 1764-1774.
- DAMIANO, D. L., QUINLIVAN, J., OWEN, B. F., SHAFFREY, M. & ABEL, M. F. 2001. Spasticity versus strength in cerebral palsy: relationships among involuntary resistance, voluntary torque, and motor function. *European Journal of Neurology*, 8 Suppl 5, 40-9.
- DARRAH, J., HICKMAN R, O'DONNELL M, VOGTLE L & L., W. 2008. *AACPDM Methodology to Develop Systematic Reviews of Treatment Interventions (Revision 1.2)*. [Online]. Available: <https://www.aacpdm.org/UserFiles/file/systematic-review-methodology.pdf> [Accessed January 2022].
- DARRAH, J., LAW, M. C., POLLOCK, N., WILSON, B., RUSSELL, D. J., WALTER, S. D., ROSENBAUM, P. & GALUPPI, B. 2011. Context therapy: a new intervention approach for children with cerebral palsy. *Developmental medicine and child neurology*, 53, 615-620.
- DAVIS, E., DAVIES, B., WOLFE, R., RAADSVELD, R., HEINE, B., THOMASON, P., DOBSON, F. & GRAHAM, H. K. 2009. A randomized controlled trial of the impact of therapeutic horse riding on the quality of life, health, and function of children with cerebral palsy. *Dev Med Child Neurol*, 51, 111-9; discussion 88.

- DAVIS, E., MACKINNON, A., DAVERN, M., BOYD, R., BOHANNA, I., WATERS, E., GRAHAM, H. K., REID, S. & REDDIHOUGH, D. 2013. Description and psychometric properties of the CP QOL-Teen: a quality of life questionnaire for adolescents with cerebral palsy. *Res Dev Disabil*, 34.
- DAVIS, E., WATERS, E., MACKINNON, A., REDDIHOUGH, D., GRAHAM, H. K., MEHMET-RADJI, O. & BOYD, R. 2006. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. *Developmental Medicine & Child Neurology*, 48, 311-318.
- DE BEUKELAER, N., WEIDE, G., HUYGHE, E., VANDEKERCKHOVE, I., HANSEN, B., PEETERS, N., UYTTERHOEVEN, J., DESCHREVEL, J., MAES, K., CORVELYN, M., COSTAMAGNA, D., GAYAN-RAMIREZ, G., VAN CAMPENHOUT, A. & DESLOOVERE, K. 2022. Reduced Cross-Sectional Muscle Growth Six Months after Botulinum Toxin Type-A Injection in Children with Spastic Cerebral Palsy. *Toxins*, 14, 139.
- DE COULON, G., CANAVESE, F., ARMAND, S., BONNEFOY-MAZURE, A. & MERLINI, L. 2022. MRI changes in calf muscles of two children with cerebral palsy following Botulinum Toxin Type A injections: a preliminary report. *Journal of pediatric orthopedics* 31, e81–e84.
- DE PAIVA, A., MEUNIER, F. A., MOLGÓ, J., AOKI, K. R. & DOLLY, J. O. 1999. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A*, 96, 3200-5.
- DELGADO, M., MATTHEWS, D., DABROWSKI, E., TILTON, A., GORMLEY, M., BONIKOWSKI, M., CARRANZA-DEL RIO, J., GRANDOULIER, A., MAHMOUD, A. & PICAUT, P. 2016a. Safety and efficacy of repeated dosing of abobotulinumtoxinA (Dysport) in children with lower limb spasticity due to cerebral palsy. *Developmental Medicine and Child Neurology*, 58, 29-30.
- DELGADO, M., TILTON, A., DURSUN, N., CARRANZADEL RIO, J., AYDIN, R., UNLU, E., ERHAN, B., RODRIGUEZ, M. & PICAUT, P. 2017a. Time to retreatment after abobotulinumtoxinA injections in children with dynamic equinus foot deformity. *Developmental Medicine and Child Neurology*, 59 (Supplement 3), 33.
- DELGADO, M. R., BONIKOWSKI, M., CARRANZA, J., DABROWSKI, E., MATTHEWS, D., RUSSMAN, B., TILTON, A., VELEZ, J. C., GRANDOULIER, A.-S. & PICAUT, P. 2017b. Safety and Efficacy of Repeat Open-Label AbobotulinumtoxinA Treatment in Pediatric Cerebral Palsy. *Journal of Child Neurology*, 32, 1058-1064.
- DELGADO, M. R., HIRTZ, D., AISEN, M., ASHWAL, S., FEHLINGS, D. L., MCLAUGHLIN, J., MORRISON, L. A., SHRADER, M. W., TILTON, A., VARGUS-ADAMS, J., DELGADO, M. R., HIRTZ, D., AISEN, M., ASHWAL, S., FEHLINGS, D. L., MCLAUGHLIN, J., MORRISON, L. A., SHRADER, M. W., TILTON, A. & VARGUS-ADAMS, J. 2010. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*, 74, 336-343.
- DELGADO, M. R., TILTON, A., RUSSMAN, B., BENAVIDES, O., BONIKOWSKI, M., CARRANZA, J., DABROWSKI, E., DURSUN, N., GORMLEY, M., JOZWIAK, M., MATTHEWS, D., MACIAG-TYMECKA, I., UNLU, E., PHAM, E., TSE, A. & PICAUT, P. 2016b. AbobotulinumtoxinA for Equinus Foot Deformity in Cerebral Palsy: A Randomized Controlled Trial. *Pediatrics*, 137, e20152830.
- DEMATTEO, C., LAW, M., RUSSELL, D., POLLOCK, N., ROSENBAUM, P. & WALTER, S. 1993. The Reliability and Validity of the Quality of Upper Extremity Skills Test. *Physical & Occupational Therapy in Pediatrics*, 13, 1-18.
- DESLOOVERE, K., DE CAT, J., MOLENAERS, G., FRANKI, I., HIMPENS, E., VAN WAELVELDE, H., FAGARD, K. & VAN DEN BROECK, C. 2012. The effect of different physiotherapy

- interventions in post-BTX-A treatment of children with cerebral palsy. *European Journal of Paediatric Neurology*, 16, 20-8.
- DESLOOVERE, K., MOLENAERS, G., DE CAT, J., PAUWELS, P., VAN CAMPENHOUT, A., ORTIBUS, E., FABRY, G. & DE COCK, P. 2007. Motor function following multilevel botulinum toxin type A treatment in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 49, 56-61.
- DESLOOVERE, K., MOLENAERS, G., JONKERS, I., DE CAT, J., DE BORRE, L., NIJS, J., EYSSEN, M., PAUWELS, P. & DE COCK, P. 2001. A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. *European journal of neurology : the official journal of the European Federation of Neurological Societies*, 8 Suppl 5, 75-87.
- DHOTE, S. N., KHATRI, P. A. & GANVIR, S. S. 2012. Reliability of "Modified timed up and go" test in children with cerebral palsy. *Journal of pediatric neurosciences*, 7, 96-100.
- DURSON, N., BONIKOWSKI, M., DABROWSKI, E., MATTHEWS, D., GORMLEY, M., TILTON, A., CARRANZA, J., GRANDOULIER, A.-S., PICAUT, P. & DELGADO, M. R. 2019. Efficacy of Repeat AbobotulinumtoxinA (Dysport®) Injections in Improving Gait in Children with Spastic Cerebral Palsy. *Developmental Neurorehabilitation*, 1-7.
- DURSON, N., DURSON, E. & ALICAN, D. 2002. The role of botulinum toxin a in the management of lower limb spasticity in patients with cerebral palsy. *International journal of clinical practice*, 56, 564-7.
- DURSON, N., GORMLEY, M., DABROWSKI, E., MATTHEWS, D., REVIVO, G., PEKER, O., ERHAN, B., KLEINSTEUBER, K., GRANDOULIER, A. S., PICAUT, P. & DELGADO, M. 2018. Effect of repeat abobotulinumtoxina injections on gait in children with dynamic equinus foot due to cerebral palsy. *Annals of Neurology*, 84 (Supplement 22), S392-S393.
- EEK, M. & HIMMELMANN, K. 2016. No decrease in muscle strength after botulinum neurotoxin-A injection in children with cerebral palsy. *Frontiers in Human Neuroscience*, 10.
- EEK, M. N., PAHLMAN, M., HIMMELMANN, K. & ASKLJUNG, B. 2014. Muscle strength after botulinum neurotoxin injection in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 56, 61-62.
- ELIASSON, A.-C., ÖHRVALL, A.-M. & BORELL, L. 2000. Parents' Perspectives of Changes in Movement Affecting Daily Life Following Selective Dorsal Rhizotomy in Children with Cerebral Palsy. *Physical & Occupational Therapy In Pediatrics*, 19, 91-109.
- ELIEGE DE SOUZA, M. N. A. C. D., RENATA CALHES FRANCO, M. F. M. S. & FABIANO POLITTI, C. S. O. 2014. Effect of Botulinum Toxin a on Spasticity and Function in Children with Cerebral Palsy: A Systematic Review. *Med Sci Tech*, 2014; 55: 11-15. Brazil.
- ELKHAYAT, S., KUMAR, R., SNEADE, C. & LITTLER, K. 2017. Categorizing goals of intramuscular botulinum toxin injection for treatment of hypertonia. *Developmental Medicine and Child Neurology*, 59 (Supplement 1), 71.
- ERIKSSON, E., HÄGGLUND, G. & ALRIKSSON-SCHMIDT, A. I. 2020. Pain in children and adolescents with cerebral palsy – a cross-sectional register study of 3545 individuals. *BMC Neurology*, 20, 15.
- EYSSEN, I. C., STEULTJENS, M. P., OUD, T. A., BOLT, E. M., MAASDAM, A. & DEKKER, J. 2011. Responsiveness of the Canadian occupational performance measure. *J Rehabil Res Dev*, 48, 517-28.
- FAGARD, K., DESLOOVERE, K., VAN DE WALLE, P. & MOLENAERS, G. 2012. The use of goal attainment scores to evaluate the effect of repeated BTX-A treatments in children with cerebral palsy. *Gait and Posture*, 36, S68-S69.
- FAIRHURST, C., SHORTLAND, A., CHANDLER, S., WILL, E., SCRUTTON, D., SIMONOFF, E. & BAIRD, G. 2019. Factors associated with pain in adolescents with bilateral cerebral palsy. *Developmental Medicine & Child Neurology*, 61, 929-936.

- FATTAL-VALEVSKI, A., DOMENIEVITZ, D., GILADI, N., WIENTROUB, S. & HAYEK, S. 2008. Long-term effect of repeated injections of botulinum toxin in children with cerebral palsy: A prospective study. *Journal of Children's Orthopaedics*, 2, 29-35.
- FEHLINGS, D., NOVAK, I., BERWECK, S., HOARE, B., STOTT, N. S. & RUSSO, R. N. 2010. Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: International consensus statement. *European Journal of Neurology*, 17, 38-56.
- FEHLINGS, D., SWITZER, L., GOLDSMITH, C., ROSENBAUM, P., WRIGHT, V., NARAYANAN, U., MESTERMAN, R., CAREY, T. & MASON, M. 2016. The long-term effectiveness of botulinum toxin A on gross motor function in ambulatory children with spastic cerebral palsy. *Developmental Medicine and Child Neurology*, 58, 25.
- FETTERS, M. D., CURRY, L. A. & CRESWELL, J. W. 2013. Achieving integration in mixed methods designs-principles and practices. *Health services research*, 48, 2134-2156.
- FIRTH, G. B., PASSMORE, E., SANGEUX, M., THOMASON, P., RODDA, J., DONATH, S., SELBER, P. & GRAHAM, H. K. 2013. Multilevel Surgery for Equinus Gait in Children with Spastic Diplegic Cerebral Palsy: Medium-Term Follow-up with Gait Analysis. *JBJS*, 95, 931-938.
- FISS, A. L., JEFFRIES, L., YOCUM, A., WESTCOTT MCCOY, S. & TEAM, T. O. T. S. 2019. Validity of the Early Activity Scale for Endurance and the 6-Minute Walk Test for Children With Cerebral Palsy. *Pediatric Physical Therapy*, 31, 156-163.
- FLEUREN, J. F. M., VOERMAN, G. E., ERREN-WOLTERS, C. V., SNOEK, G. J., RIETMAN, J. S., HERMENS, H. J. & NENE, A. V. 2010. Stop using the Ashworth Scale for the assessment of spasticity. *Journal of Neurology, Neurosurgery & Psychiatry*, 81, 46-52.
- FORTUNA, R., HORISBERGER, M., VAZ, M. A. & HERZOG, W. 2013. Do skeletal muscle properties recover following repeat onabotulinum toxin A injections? *Journal of Biomechanics*, 46, 2426-2433.
- FOSANG, A. L., GALEA, M. P., MCCOY, A. T., REDDIHOUGH, D. S. & STORY, I. 2003. Measures of muscle and joint performance in the lower limb of children with cerebral palsy. *Developmental Medicine & Child Neurology*, 45, 664-670.
- FRAGALA, M. A., O'NEIL M, E., RUSSO, K. J. & DUMAS, H. M. 2002. Impairment, disability, and satisfaction outcomes after lower-extremity botulinum toxin a injections for children with cerebral palsy. *Pediatr Phys Ther*, 14, 132-44.
- FRANKI, I., BAR-ON, L., MOLENAERS, G., VAN CAMPENHOUT, A., CRAENEN, K., DESLOOVERE, K., FEYS, H., PAUWELS, P., DE CAT, J. & ORTIBUS, E. 2020. Tone Reduction and Physical Therapy: Strengthening Partners in Treatment of Children with Spastic Cerebral Palsy. *Neuropediatrics*, 51, 89-104.
- FRANKI, I., DESLOOVERE, K., DE CAT, J., TIJHUIS, W., MOLENAERS, G., FEYS, H., VANDERSTRAETEN, G. & VAN DEN BROECK, C. 2015. An evaluator-blinded randomized controlled trial evaluating therapy effects and prognostic factors for a general and an individually defined physical therapy program in ambulant children with bilateral spastic cerebral palsy. *European journal of physical & rehabilitation medicine.*, 51, 677-91.
- FRANZEN, M., HÄGGLUND, G. & ALRIKSSON-SCHMIDT, A. 2017. *BMC Musculoskelet Disord*, 18, 520.
- FRASCARELLI, F., DI ROSA, G., BISOZZI, E., CASTELLI, E. & SANTILLI, V. 2011. Neurophysiological changes induced by the botulinum toxin type A injection in children with cerebral palsy. *European Journal of Paediatric Neurology*, 15, 59-64.
- FRIEDMAN, B.-C. & GOLDMAN, R. D. 2011. Use of botulinum toxin A in management of children with cerebral palsy. *Canadian family physician Medecin de famille canadien*, 57, 1006-1073.

- FUGARD, A. J. B. & POTTS, H. W. W. 2015. Supporting thinking on sample sizes for thematic analyses: a quantitative tool. *International Journal of Social Research Methodology*, 18, 669-684.
- GARNIER-VILLARREAL, M., RHEMTULLA, M. & LITTLE, T. D. 2014. Two-method planned missing designs for longitudinal research. *International Journal of Behavioral Development*, 38, 411-422.
- GIBSON, B. E., TEACHMAN, G., WRIGHT, V., FEHLINGS, D., YOUNG, N. L. & MCKEEVER, P. 2012. Children's and parents' beliefs regarding the value of walking: rehabilitation implications for children with cerebral palsy. *Child Care Health Dev*, 38, 61-9.
- GIBSON, N., CHAPPELL, A., BLACKMORE, A. M., MORRIS, S., WILLIAMS, G., BEAR, N. & ALLISON, G. 2018. The effect of a running intervention on running ability and participation in children with cerebral palsy: a randomized controlled trial. *Disabil Rehabil*, 40, 3041-3049.
- GILADI, N. 1997. The mechanism of action of botulinum toxin type A in focal dystonia is most probably through its dual effect on efferent (motor) and afferent pathways at the injected site. *Journal of the neurological sciences*, 152, 132-135.
- GOODALL, J. & MONTGOMERY, C. 2014. Parental involvement to parental engagement: a continuum. *Educational Review*, 66, 399-410.
- GORDON, A. L. 2014. Functioning and disability after stroke in children: using the ICF-CY to classify health outcome and inform future clinical research priorities. *Dev Med Child Neurol*, 56, 434-44.
- GOUGH, M. 2009. Does botulinum toxin prevent or promote deformity in children with cerebral palsy? *Developmental Medicine & Child Neurology*, 51, 89-90.
- GRAHAM, H. K., BOYD, R., CARLIN, J. B., DOBSON, F., LOWE, K., NATTRASS, G., THOMASON, P., WOLFE, R. & REDDIHOUGH, D. 2008. Does botulinum toxin a combined with bracing prevent hip displacement in children with cerebral palsy and "hips at risk"? A randomized, controlled trial. *Journal of Bone & Joint Surgery - American Volume*, 90, 23-33.
- GRAHAM, H. K., ROSENBAUM, P., PANETH, N., DAN, B., LIN, J. P., DAMIANO, D. L., BECHER, J. G., GAEBLER-SPIRA, D., COLVER, A., REDDIHOUGH, D., CROMPTON, K. E. & LIEBER, R. L. 2016. Cerebral palsy. *Nature Reviews Disease Primers*, 2.
- GUYOT, P., KALYVAS, C., MAMANE, C. & DANCHENKO, N. 2019. Botulinum Toxins Type A (Bont-A) in the Management of Lower Limb Spasticity in Children: A Systematic Literature Review and Bayesian Network Meta-analysis. *Journal of Child Neurology*.
- HALEY, S. M. & FRAGALA-PINKHAM, M. A. 2006. Interpreting Change Scores of Tests and Measures Used in Physical Therapy. *Physical Therapy*, 86, 735-743.
- HALMA, E., BUSSMANN, J. B. J., VAN DEN BERG-EMONS, H. J. G., SNEEKES, E. M., PANGALILA, R., SCHASFOORT, F. C. & GROUP, O. B. O. T. S. B. S. 2020. Relationship between changes in motor capacity and objectively measured motor performance in ambulatory children with spastic cerebral palsy. *Child: Care, Health and Development*, 46, 66-73.
- HANNA, S., ROSENBAUM, P., BARTLETT, D., PALISANO, R., D WALTER, S., AVERY, L. & RUSSELL, D. 2009. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. *Developmental medicine and child neurology*, 51, 295-302.
- HASSANI, S., KRZAK, J. J., JOHNSON, B., FLANAGAN, A., GORTON III, G., BAGLEY, A., ÖUNPUU, S., ROMNESS, M., TYLKOWSKI, C. & OEFFINGER, D. 2014. One-Minute Walk and modified Timed Up and Go tests in children with cerebral palsy: performance and minimum clinically important differences. *Developmental Medicine & Child Neurology*, 56, 482-489.
- HASTINGS-ISON, T., BLACKBURN, C., GRAHAM, H. K., RAWICKI, B., FAHEY, M., SIMPSON, P. & BAKER, R. 2014. Optimum frequency of botulinum toxin injections to the

- gastrocsoleus in children with cerebral palsy-a randomised controlled trial. *Developmental Medicine and Child Neurology*, 56, 27.
- HASTINGS-ISON, T., BLACKBURN, C., RAWICKI, B., FAHEY, M., SIMPSON, P., BAKER, R. & GRAHAM, K. 2016. Injection frequency of botulinum toxin A for spastic equinus: a randomized clinical trial. *Developmental medicine and child neurology*, 58, 750-7.
- HASTINGS-ISON, T., SANGEUX, M. & GRAHAM, H. 2017. Botulinum Toxin A injections for spastic equinus in ambulant children with cerebral palsy: Longterm follow-up and time to surgery. *Developmental Medicine and Child Neurology*, 59 (Supplement 3), 33-34.
- HASTINGS-ISON, T., SANGEUX, M., THOMASON, P., RAWICKI, B., FAHEY, M. & GRAHAM, H. K. 2018. Onabotulinum toxin-A (Botox) for spastic equinus in cerebral palsy: a prospective kinematic study. *Journal of children's orthopaedics*, 12, 390-397.
- HEINEN, F., DESLOOVERE, K., SCHROEDER, A. S., BERWECK, S., BORGGRAEFE, I., VAN CAMPENHOUT, A., ANDERSEN, G. L., AYDIN, R., BECHER, J. G., BERNERT, G., CABALLERO, I. M., CARR, L., VALAYER, E. C., DESIATO, M. T., FAIRHURST, C., FILIPETTI, P., HASSINK, R. I., HUSTEDT, U., JOZWIAK, M., KOCER, S. I., KOLANOWSKI, E., KRÄGELOH-MANN, I., ŞEHİM, K., MÄENPÄÄ, H., MALL, V., MCARTHUR, P., MOREL, E., PAPAVALASSIOU, A., PASCUAL-PASCUAL, I., PEDERSEN, S. A., PLASSCHAERT, F. S., IRENE VAN DER, P., REMY-NERIS, O., RENDERS, A., DI ROSA, G., STEINLIN, M., TEDROFF, K., VALLS, J. V., VIEHWEGER, E. & MOLENAERS, G. 2010. The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. *European Journal of Paediatric Neurology*, 14, 45-66.
- HEINEN, F., KAŇOVSKÝ, P., SCHROEDER, A. S., CHAMBERS, H. G., DABROWSKI, E., GEISTER, T. L., HANSCHMANN, A., MARTINEZ-TORRES, F. J., PULTE, I., BANACH, M. & GAEBLER-SPIRA, D. 2021. IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study. *J Pediatr Rehabil Med*, 14, 183-197.
- HEYVAERT, M., MAES, B. & ONGHENA, P. 2013. Mixed methods research synthesis: definition, framework, and potential. *Quality & Quantity*, 47, 659-676.
- HICKS, C. L., VON BAEYER, C. L., SPAFFORD, P. A., VAN KORLAAR, I. & GOODENOUGH, B. 2001. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*, 93, 173-83.
- HOARE, B. J., WALLEN, M. A., IMMS, C., VILLANUEVA, E., RAWICKI, H. B. & CAREY, L. 2010. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). *Cochrane Database of Systematic Reviews*, N.PAG-N.PAG.
- HOK, P., VEVERKA, T., HLUŠTÍK, P., NEVRLÝ, M. & KAŇOVSKÝ, P. 2021. The Central Effects of Botulinum Toxin in Dystonia and Spasticity. *Toxins*, 13, 155.
- HOLSBEEKE, L., KETELAAR, M., SCHOEMAKER, M. M. & GORTER, J. W. 2009. Capacity, capability, and performance: different constructs or three of a kind? *Arch Phys Med Rehabil*, 90, 849-55.
- HONAN, I., FINCH-EDMONDSON, M., IMMS, C., NOVAK, I., HOGAN, A., CLOUGH, S., BONYHADY, B., MCINTYRE, S., ELLIOTT, C., WONG, S., BINK, M. & BADAWI, N. 2022. Is the search for cerebral palsy 'cures' a reasonable and appropriate goal in the 2020s? *Dev Med Child Neurol*, 64, 49-55.
- HORSTMAN, M., ALDISS, S., RICHARDSON, A. & GIBSON, F. 2008. Methodological Issues When Using the Draw and Write Technique With Children Aged 6 to 12 Years. *Qualitative Health Research*, 18, 1001-1011.
- IBM CORP 2020. IBM SPSS Statistics for Windows, Version 27.0. In: CORP, I. (ed.). Armonk, NY.

- IBRAHIM, A. I., HAWAMDEH, Z. M. & AL-QUDAH, A. A. 2007. Functional outcome of botulinum toxin injection of gastrocnemius and adductors in spastic hemiplegic cerebral palsied children. *Europa Medicophysica*, 43, 13-20.
- IMMS, C., GRANLUND, M., WILSON, P. H., STEENBERGEN, B., ROSENBAUM, P. L. & GORDON, A. M. 2017. Participation, both a means and an end: a conceptual analysis of processes and outcomes in childhood disability. *Developmental Medicine & Child Neurology*, 59, 16-25.
- IMMS, C., MATHEWS, S., RICHMOND, K. N., LAW, M. & ULLENHAG, A. 2016. Optimising leisure participation: a pilot intervention study for adolescents with physical impairments. *Disabil Rehabil*, 38, 963-71.
- INAGI, K., CONNOR, N. P., SCHULTZ, E., FORD, C. N., COOK, C. H. & HEISEY, D. M. 1999. Muscle fiber-type changes induced by botulinum toxin injection in the rat larynx. *Otolaryngol Head Neck Surg*, 120, 876-83.
- INVOLVE 2016. Involving children and young people in research: Top tips and essential key issues for researchers. *INVOLVE, Eastleigh*
- JANKOVIC, J. 2017. Botulinum toxin: State of the art. *Movement Disorders*, 32, 1131-1138.
- JANSSEN, A. J. W. M., DIEKEMA, E. T. W., VAN DOLDER, R., KOLLÉE, L. A. A., OOSTENDORP, R. A. B. & NIJHUIS-VAN DER SANDEN, M. W. G. 2012. Development of a Movement Quality Measurement Tool for Children. *Physical Therapy*, 92, 574-594.
- JENSEN, D. B., KLINGENBERG, S., DIMINTIYANOVA, K. P., WIENECKE, J. & MEEHAN, C. F. 2020. Intramuscular Botulinum toxin A injections induce central changes to axon initial segments and cholinergic boutons on spinal motoneurons in rats. *Scientific Reports*, 10, 893.
- JETTE, A. M. 2020. Opening the Black Box of Rehabilitation Interventions. *Physical Therapy*, 100, 883-884.
- JETTE, A. M. & HALEY, S. M. 2005. Contemporary measurement techniques for rehabilitation outcomes assessment. *J Rehabil Med*, 37, 339-45.
- JOHNSON, R. B., ONWUEGBUZIE, A. J. & TURNER, L. A. 2007. Toward a Definition of Mixed Methods Research. *Journal of Mixed Methods Research*, 1, 112-133.
- JOHNSTON, C. C. & VON BAEYER, C. L. 2012. A measure of pediatric pain intensity across ages and clinical conditions. *PAIN*, 153.
- JOHNSTON, K., DANCHENKO, N., HANSEN, R., DINET, J., LIOVAS, A., ARMSTRONG, A., BAINS, S. & SULLIVAN, S. D. 2020. Cost effectiveness and impact on quality of life of abobotulinumtoxinA and onabotulinumtoxinA in the treatment of children with lower limb spasticity in Canada. *J Med Econ*, 23, 631-640.
- KAHRAMAN, A., SEYHAN, K., DEGER, U., KUTLUTURK, S. & MUTLU, A. 2016. Should botulinum toxin A injections be repeated in children with cerebral palsy? A systematic review. *Developmental Medicine and Child Neurology*, 58, 910-917.
- KALKMAN, B. M., BAR-ON, L., O'BRIEN, T. D. & MAGANARIS, C. N. 2020. Stretching Interventions in Children With Cerebral Palsy: Why Are They Ineffective in Improving Muscle Function and How Can We Better Their Outcome? *Frontiers in Physiology*, 11.
- KANG, M., SMITH, E., GOLDSMITH, C. H., SWITZER, L., ROSENBAUM, P., WRIGHT, F. V. & FEHLINGS, D. 2020. Documenting change with the Canadian Occupational Performance Measure for children with cerebral palsy. *Developmental Medicine and Child Neurology*, 62, 1154-1160.
- KANOVSKY, P., BARES, M., RICHARDSON, A., KRAUS, J., SEVERA, S., TURCONI, A. C., BONIKOWSKI, M., JASINSKI, M., JOZWIAK, M., LUKASZEWSKA, A., TYMECKA-MACIAG, I., WENDORFF, J., BENETIN, J., LISY, L., CARDO, E., MACAYA, A., PASCUAL, S. I. P., POO, P., FONTAN, D. & MORTON, R. 2009. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-

- limb spasticity in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 51, 436-445.
- KATCHBURIAN, L., R., CAWKER S, COOMBE S, KINLEY E, SHAW R, WIGGINS L & E, W. 2008. *Use of Botulinum Toxin in Children with Neurological Conditions*, London UK, Association of Paediatric Chartered Physiotherapists (APCP).
- KATCHBURIAN, L. R. 1997. An Investigation into the Effect of Botulinum Toxin A on Motor Function in the Child with Cerebral Palsy [Unpublished MSc Thesis]. London: University of East London
- KAZDIN, A. E. 1977. ARTIFACT, BIAS, AND COMPLEXITY OF ASSESSMENT: THE ABCs OF RELIABILITY. *Journal of Applied Behavior Analysis*, 10, 141-150.
- KELLY, B., MACKAY-LYONS, M., BERRYMAN, S., HYNDMAN, J. & WOOD, E. 2019. Casting Protocols Following BoNT-A Injections to Treat Spastic Hypertonia of the Triceps Surae in Children with Cerebral Palsy and Equinus Gait: A Randomized Controlled Trial. *Physical & Occupational Therapy in Pediatrics*, 39, 77-93.
- KHETANI, M. A., CLIFF, A. B., SCHELLY, C., DAUNHAUER, L. & ANABY, D. 2015. Decisional Support Algorithm for Collaborative Care Planning using the Participation and Environment Measure for Children and Youth (PEM-CY): A Mixed Methods Study. *Physical & Occupational Therapy In Pediatrics*, 35, 231-252.
- KING, G., LAW, M., KING, S., ROSENBAUM, P., KERTOY, M. K. & YOUNG, N. L. 2003. A conceptual model of the factors affecting the recreation and leisure participation of children with disabilities. *Phys Occup Ther Pediatr*, 23, 63-90.
- KO, J. & KIM, M. 2012. Inter-rater Reliability of the K-GMFM-88 and the GMPM for Children with Cerebral Palsy. *Annals of rehabilitation medicine*, 36, 233-239.
- KOBAK, K. A., ENGELHARDT, N., WILLIAMS, J. B. W. & LIPSITZ, J. D. 2004. Rater Training in Multicenter Clinical Trials: Issues and Recommendations. *Journal of Clinical Psychopharmacology*, 24, 113-117.
- KOMAN, L. A., BRASHEAR, A., ROSENFELD, S., CHAMBERS, H., RUSSMAN, B., RANG, M., ROOT, L., FERRARI, E., PROUS, J. G. D., SMITH, B. P., TURKEL, C., WALCOTT, J. M. & MOLLOY, P. T. 2001. Botulinum toxin type A neuromuscular blockage in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics*, 108, 1062-1071.
- KOMAN, L. A., MOONEY, I. J. F., SMITH, B., GOODMAN, A. & MULVANEY, T. 1993. Management of cerebral palsy with botulinum-A toxin: Preliminary investigation. *Journal of Pediatric Orthopaedics*, 13, 489-495.
- KOMAN, L. A., MOONEY, J. F., 3RD, SMITH, B. P., GOODMAN, A. & MULVANEY, T. 1994. Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial. *Journal of Pediatric Orthopaedics*, 14, 299-303.
- KOMAN, L. A., PATERSON SMITH, B. & BALKRISHNAN, R. 2003. Spasticity associated with cerebral palsy in children: guidelines for the use of botulinum A toxin. *Paediatric Drugs*, 5, 11-23.
- KOO, T. K. & LI, M. Y. 2016. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of chiropractic medicine*, 15, 155-163.
- KOOG, Y. H. & MIN, B. 2010. Effects of botulinum toxin A on calf muscles in children with cerebral palsy: a systematic review. *Clinical Rehabilitation*, 24, 685-700.
- KRAUS DE CAMARGO, O., SIMON L, RONEN GM & PL, R. 2019. *ICF: A hands-on approach for clinicians and families.* , London Mac Keith Press.
- KRIEGER, B., SCHULZE, C., BOYD, J., AMANN, R., PIŠKUR, B., BEURSKENS, A., TEPLICKY, R. & MOSER, A. 2020. Cross-cultural adaptation of the Participation and Environment Measure for Children and Youth (PEM-CY) into German: a qualitative study in three countries. *BMC Pediatrics*, 20, 492.

- KUZNETSOVA, A., BROCKHOFF, P. B. & CHRISTENSEN, R. H. B. 2017. ImerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, 82, 1 - 26.
- LAERD STATISTICS. 2015. *One-way repeated measures ANOVA using SPSS Statistics* [Online]. Available: <https://statistics.laerd.com/>.
- LAMANNA, C. 1959. The most poisonous poison. *Science*, 130, 763-72.
- LANCE, J. W. 1980. Pathophysiology of Spasticity and Clinical Experience with Baclofen. *Lance, J.W., Feldman, R.G., Young, R.R. and Koella, W.P., Eds., Spasticity: Disordered Motor Control, Year Book, Chicago*, 185-204.
- LAW, M., ANABY, D., IMMS, C., TEPLICKY, R. & TURNER, L. 2015. Improving the participation of youth with physical disabilities in community activities: An interrupted time series design. *Australian Occupational Therapy Journal*, 62, 105-115.
- LAW, M., BAPTISTE, S., CARSWELL, A., MCCOLL, M., POLATAJKO, H. & POLLOCK, N. 2019. *The Canadian Occupational Performance Measure*, Altona, CAOT Publications ACE.
- LAW, M., BAPTISTE, S., CARSWELL, A., MCCOLL, M. A., POLATAJKO, H. & POLLOCK, N. 2005. *Canadian Occupational Performance Measure*. Ottawa: CAOT Publications ACE.
- LAW, M., BAPTISTE, S. & MILLS, J. 1995a. Client-centred practice: what does it mean and does it make a difference? *Can J Occup Ther*, 62, 250-7.
- LAW, M., BAPTISTE, S. & MILLS, J. 1995b. Client-Centred Practice: What does it Mean and Does it Make a Difference? *Canadian Journal of Occupational Therapy*, 62, 250-257.
- LAW, M., HANNA, S., KING, G., HURLEY, P., KING, S., KERTOY, M. & ROSENBAUM, P. 2003. Factors affecting family-centred service delivery for children with disabilities. *Child: Care, Health and Development*, 29, 357-366.
- LEE, D., KIM, J., OH, J. Y., HAN, M. H., KIM, D. Y., KANG, J. H. & JANG, D. H. 2021. Changes in Muscle Mass after Botulinum Toxin Injection in Children with Spastic Hemiplegic Cerebral Palsy. *Toxins (Basel)*, 13.
- LEGERLOTZ, K., MATTHEWS, K. G., MCMAHON, C. D. & SMITH, H. K. 2009. Botulinum toxin-induced paralysis leads to slower myosin heavy chain isoform composition and reduced titin content in juvenile rat gastrocnemius muscle. *Muscle & Nerve*, 39, 472-479.
- LINDER-LUCHT, M., KIRSCHNER, J., HERRMANN, J., GETH, K., KORINTHENBERG, R., BERWECK, S., HEINEN, F. & MALL, V. 2006. Why do children with cerebral palsy discontinue therapy with botulinum toxin A? *Developmental Medicine and Child Neurology*, 48, 319-320.
- LINDER, M., SCHINDLER, G., MICHAELIS, U., STEIN, S., KIRSCHNER, J., MALL, V., BERWECK, S., KORINTHENBERG, R. & HEINEN, F. 2001. Medium-term functional benefits in children with cerebral palsy treated with botulinum toxin type A: 1-year follow-up using gross motor function measure. *European journal of neurology : the official journal of the European Federation of Neurological Societies*, 8 Suppl 5, 120-126.
- LONGO, E., GALVÃO, É., CAMPOS, A., LOPES, P., OLIVEIRA, A. & CAZEIRO, A. 2019. Transcultural adaptation and validation for use in Brazil of the Participation and Environment Measure – Children and Youth (PEM-CY). *Developmental Medicine & Child Neurology*, 61, 8-9.
- LORIN, K. & FORSBERG, A. 2016. Treatment with botulinum toxin in children with cerebral palsy: a qualitative study of parents' experiences. *Child Care Health and Development*, 42, 494-503.
- LOVE, S., COLE, J., VALENTINE, J. & BLAIR, E. 2010a. Should we be using botulinum toxin earlier? *Developmental Medicine and Child Neurology*, 52, 35.
- LOVE, S. C., NOVAK, I., KENTISH, M., DESLOOVERE, K., HEINEN, F., MOLENAERS, G., O'FLAHERTY, S. & GRAHAM, H. K. 2010b. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: International consensus statement. *European Journal of Neurology*, 17, 9-37.

- LOVE, S. C., VALENTINE, J. P., BLAIR, E. M., PRICE, C. J., COLE, J. H. & CHAUVEL, P. J. 2001. The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. *European Journal of Neurology*, 8 Suppl 5, 50-8.
- LOWING, K., BEXELIUS, A. & CARLBERG, E. B. 2010. Goal-directed functional therapy: A longitudinal study on gross motor function in children with cerebral palsy. *Disability and Rehabilitation*, 32, 908-916.
- LOWING, K., THEWS, K., HAGLUND-AKERLIND, Y. & GUTIERREZ-FAREWIK, E. M. 2017. Effects of Botulinum Toxin-A and Goal-Directed Physiotherapy in Children with Cerebral Palsy GMFCS Levels I & II. *Physical & Occupational Therapy in Pediatrics*, 37, 268-282.
- LÖWING, K., THEWS, K., HAGLUND-ÅKERLIND, Y. & GUTIERREZ-FAREWIK, E. M. 2017. Effects of Botulinum Toxin-A and Goal-Directed Physiotherapy in Children with Cerebral Palsy GMFCS Levels I & II. *Physical & Occupational Therapy in Pediatrics*, 37, 268-282.
- LUKBAN, M. B., ROSALES, R. L. & DRESSLER, D. 2009. Effectiveness of botulinum toxin A for upper and lower limb spasticity in children with cerebral palsy: a summary of evidence. *Journal of Neural Transmission*, 116, 319-331.
- MACLENNAN, A. H., THOMPSON, S. C. & GECZ, J. 2015. Cerebral palsy: causes, pathways, and the role of genetic variants. *American Journal of Obstetrics and Gynecology*, 213, 779-788.
- MAJNEMER, A., SHEVELL, M., LAW, M., POULIN, C. & ROSENBAUM, P. 2012. Indicators of distress in families of children with cerebral palsy. *Disability and Rehabilitation*, 34, 1202-1207.
- MAKRIS, T., DORSTYN, D. & CRETENDEN, A. 2021. Quality of life in children and adolescents with cerebral palsy: a systematic review with meta-analysis. *Disabil Rehabil*, 43, 299-308.
- MALTERUD, K., SIERSMA, V. D. & GUASSORA, A. D. 2016. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qualitative Health Research*, 26, 1753-1760.
- MANDALESON, A., LEE, Y., KERR, C. & GRAHAM, H. K. 2014. Classifying cerebral palsy: Are we nearly there? *Developmental Medicine and Child Neurology*, 56, 71.
- MARDER, E., JORGE-RIVERA, J., KILMAN, V., WEIMANN, J., FESTOFF, B., HANTAI, D. & CITRON, B. 1997. The synapse: in development, health, and disease.
- MATAK, I. & LACKOVIĆ, Z. 2015. Botulinum neurotoxin type A: Actions beyond SNAP-25? *Toxicology*, 335, 79-84.
- MATHESON, G. J. 2019. We need to talk about reliability: making better use of test-retest studies for study design and interpretation. *PeerJ*, 7, e6918-e6918.
- MATHEVON, L., BONAN, I., BARNAIS, J. L., BOYER, F. & DINOMAIS, M. 2019. Adjunct therapies to improve outcomes after botulinum toxin injection in children: A systematic review. *Ann Phys Rehabil Med*, 62, 283-290.
- MATHEVON, L., MICHEL, F., DECAVEL, P., FERNANDEZ, B., PARRATTE, B. & CALMELS, P. 2015. Muscle structure and stiffness assessment after botulinum toxin type A injection. A systematic review. *Ann Phys Rehabil Med*, 58, 343-50.
- MATHEWSON, M. A. & LIEBER, R. L. 2015. Pathophysiology of Muscle Contractures in Cerebral Palsy. *Physical Medicine and Rehabilitation Clinics of North America*, 26, 57-67.
- MATHISON, S. 2005. Encyclopedia of Evaluation.
- MATTHEWS, D., CAMBA, G. C., PASCUAL-PASCUAL, I., TILTON, A. H., GORMLEY, M., MAHMOOD, A., PICAUT, P., SNYDER, D. & DELGADO, M. R. 2016. Safety and tolerability of abobotulinumtoxin A (dysport) in children (2-17 years) with lower limb

- spasticity due to cerebral palsy: A pooled analysis of 8 clinical trials. *PM and R*, 8 (9 Supplement), S318.
- MAZEN, J. A. M., TONG, X. & TAYLOR, L. K. 2019. Evaluation of supplemental samples in longitudinal research with non-normal missing data. *Behavior Research Methods*, 51, 1321-1335.
- MCCOLL, M. A., LAW, M., BAPTISTE, S., POLLOCK, N., CARSWELL, A. & POLATAJKO, H. J. 2005. Targeted Applications of the Canadian Occupational Performance Measure. *Canadian Journal of Occupational Therapy*, 72, 298-300.
- MCDOWELL, B. C., HEWITT, V., NURSE, A., WESTON, T. & BAKER, R. 2000. The variability of goniometric measurements in ambulatory children with spastic cerebral palsy. *Gait Posture*, 12, 114-21.
- MCDOWELL, B. C., KERR, C., PARKES, J. & COSGROVE, A. 2005. Validity of a 1 minute walk test for children with cerebral palsy. *Dev Med Child Neurol*, 47.
- MCKINNON, C. T., MEEHAN, E. M., HARVEY, A. R., ANTOLOVICH, G. C. & MORGAN, P. E. 2019. Prevalence and characteristics of pain in children and young adults with cerebral palsy: a systematic review. *Dev Med Child Neurol*, 61, 305-314.
- MCLEOD, L. D., COON, C. D., MARTIN, S. A., FEHNEL, S. E. & HAYS, R. D. 2011. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Review of Pharmacoeconomics & Outcomes Research*, 11, 163-169.
- MCMORRAN, D., ROBINSON, L. W., HENDERSON, G., HERMAN, J., ROBB, J. E. & GASTON, M. S. 2016. Using a goal attainment scale in the evaluation of outcomes in patients with diplegic cerebral palsy. *Gait Posture*, 44, 168-71.
- METAXIOTIS, D., SIEBEL, A. & DOEDERLEIN, L. 2002. Repeated botulinum toxin A injections in the treatment of spastic equinus foot. *Clinical Orthopaedics & Related Research*, 394, 177-185.
- MICHELSEN, J. S., NORMANN, G. & WONG, C. 2018. Analgesic Effects of Botulinum Toxin in Children with CP. *Toxins*, 10.
- MINAMOTO, V. B., SUZUKI, K. P., BREMNER, S. N., LIEBER, R. L. & WARD, S. R. 2015. Dramatic changes in muscle contractile and structural properties after 2 botulinum toxin injections. *Muscle & Nerve*, 52, 649-657.
- MISRA, A. K., KUMAR, S., BISWAS, B. A. & DAS, S. K. 2010. Botulinum toxin type A in subjects with spastic cerebral palsy from Eastern India. *Journal of Pediatric Neurology*, 8, 349-357.
- MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. & THE, P. G. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine*, 6, e1000097.
- MOLENAERS, G., DESLOOVERE, K., DE CAT, J., JONKERS, I., DE BORRE, L., PAUWELS, P., NIJS, J., FABRY, G. & DE COCK, P. 2001. Single event multilevel botulinum toxin type A treatment and surgery: similarities and differences. *European journal of neurology : the official journal of the European Federation of Neurological Societies*, 8 Suppl 5, 88-97.
- MOLENAERS, G., FAGARD, K., VAN CAMPENHOUT, A. & DESLOOVERE, K. 2013. Botulinum toxin A treatment of the lower extremities in children with cerebral palsy. *J Child Orthop*, 7, 383-7.
- MOLENAERS, G., SCHORKHUBER, V., FAGARD, K., VAN CAMPENHOUT, A., DE CAT, J., PAUWELS, P., ORTIBUS, E., DE COCK, P. & DESLOOVERE, K. 2009. Long-term use of botulinum toxin type A in children with cerebral palsy: treatment consistency. *European Journal of Paediatric Neurology*, 13, 421-9.
- MOLENAERS, G., VAN CAMPENHOUT, A., FAGARD, K., DE CAT, J. & DESLOOVERE, K. 2010. The use of botulinum toxin A in children with cerebral palsy, with a focus on the lower limb. *Journal of Children's Orthopaedics*, 4, 183-195.

- MORRIS, C., KURINCZUK, J. J. & FITZPATRICK, R. 2005. Child or family assessed measures of activity performance and participation for children with cerebral palsy: a structured review. *Child: Care, Health and Development*, 31, 397-407.
- MORRIS, C., SIMKISS, D., BUSK, M., MORRIS, M., ALLARD, A., DENNESS, J., JANSSENS, A., STIMSON, A., COGHILL, J., ROBINSON, K., FENTON, M. & COWAN, K. 2015. Setting research priorities to improve the health of children and young people with neurodisability: a British Academy of Childhood Disability-James Lind Alliance Research Priority Setting Partnership. *BMJ Open*, 5, e006233.
- MORSE, J. M. & NIEHAUS, L. 2009. *Mixed Method Design: Principles and Procedures*, Walnut Creek, CA, USA, Left Coast Press Inc.
- MPUNDU-KAAMBWA, C., CHEN, G., DALZIEL, K., DEVLIN, N. & RATCLIFFE, J. 2021. International guidelines for self-report and proxy completion of paediatric health-related quality of life measures: a protocol for a systematic review. *BMJ Open*, 11, e052049.
- MSALL, M. E., AVERY, R. C., TREMONT, M. R., LIMA, J. C., ROGERS, M. L. & HOGAN, D. P. 2003. Functional disability and school activity limitations in 41,300 school-age children: relationship to medical impairments. *Pediatrics*, 111, 548-53.
- MUGGLESTONE, M. A., EUNSON, P., MURPHY, M. S. & GUIDELINE DEVELOPMENT, G. 2012. Spasticity in children and young people with non-progressive brain disorders: summary of NICE guidance. *BMJ*, 345, e4845.
- MULTANI, I., MANJI, J., HASTINGS-ISON, T., KHOT, A. & GRAHAM, K. 2019a. Botulinum Toxin in the Management of Children with Cerebral Palsy. *Paediatr Drugs*, 21, 261-281.
- MULTANI, I., MANJI, J., TANG, M. J., HERZOG, W., HOWARD, J. J. & GRAHAM, H. K. 2019b. Sarcopenia, Cerebral Palsy, and Botulinum Toxin Type A. *JBJS Rev*, 7, e4.
- MUTLU, A., LIVANELIOGLU, A. & GUNEL, M. K. 2008. Reliability of Ashworth and Modified Ashworth Scales in Children with Spastic Cerebral Palsy. *BMC Musculoskeletal Disorders*, 9, 44.
- NEY, J. P. & JOSEPH, K. R. 2007. Neurologic uses of botulinum neurotoxin type A. *Neuropsychiatr Dis Treat*, 3, 785-98.
- NGUYEN, L., DI REZZE, B., MESTERMAN, R., ROSENBAUM, P. & GORTER, J. W. 2018. Effects of Botulinum Toxin Treatment in Nonambulatory Children and Adolescents With Cerebral Palsy: Understanding Parents' Perspectives. *Journal of Child Neurology*, 33, 724-733.
- NGUYEN, L., MESTERMAN, R. & GORTER, J. 2016. Development of an inventory of goals using the international classification of functioning, disability and Health in a population of nonambulatory children and adolescents with cerebral palsy treated with botulinum toxin A. *Developmental Medicine and Child Neurology*, 58, 76-77.
- NICE 2012. Spasticity in children and young people with non progressive brain disorders. *Clinical Guideline 145*; . London: National Institute for Health and Clinical Excellence. .
- NIEUWENHUYNS, A., PAPAGEORGIOU, E., PATAKY, T., DE LAET, T., MOLENAERS, G. & DESLOOVERE, K. 2016. Literature Review and Comparison of Two Statistical Methods to Evaluate the Effect of Botulinum Toxin Treatment on Gait in Children with Cerebral Palsy. *PLoS ONE [Electronic Resource]*, 11, e0152697.
- NOVAK, I. 2014. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. *J Child Neurol*, 29, 1141-56.
- NOVAK, I., MCINTYRE, S., MORGAN, C., CAMPBELL, L., DARK, L., MORTON, N., STUMBLES, E., WILSON, S. A. & GOLDSMITH, S. 2013. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol*, 55, 885-910.
- NOVAK, I., MORGAN, C., FAHEY, M., FINCH-EDMONDSON, M., GALEA, C., HINES, A., LANGDON, K., NAMARA, M. M., PATON, M. C., POPAT, H., SHORE, B., KHAMIS, A.,

- STANTON, E., FINEMORE, O. P., TRICKS, A., TE VELDE, A., DARK, L., MORTON, N. & BADAWI, N. 2020. State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy. *Curr Neurol Neurosci Rep*, 20, 3.
- NUMANOĞLU, A. & GÜNEL, M. K. 2012. Intraobserver reliability of modified Ashworth scale and modified Tardieu scale in the assessment of spasticity in children with cerebral palsy. *Acta Orthop Traumatol Turc*, 46, 196-200.
- O'FLAHERTY, S., JANAKAN, V., MORROW, A. M., SCHEINBERG, A. M. & WAUGH, M. A. 2011. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 53, 125-130.
- O'GRADY, M. G. & DUSING, S. C. 2015. Reliability and Validity of Play-Based Assessments of Motor and Cognitive Skills for Infants and Young Children: A Systematic Review. *Physical Therapy*, 95, 25-38.
- O'NEIL, M. E., FRAGALA, M. A. & DUMAS, H. M. 2003. Physical therapy intervention for children with cerebral palsy who receive botulinum toxin a injections. *Pediatr Phys Ther*, 15, 204-15.
- ODDING, E., ROEBROECK, M. E. & STAM, H. J. 2006. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil*, 28, 183-91.
- OEFFINGER, D., BAGLEY, A., ROGERS, S., GORTON, G., KRYSICIO, R., ABEL, M., DAMIANO, D., BARNES, D. & TYLKOWSKI, C. 2008. Outcome tools used for ambulatory children with cerebral palsy: responsiveness and minimum clinically important differences. *Dev Med Child Neurol*, 50, 918-25.
- OSTENSJØ, S., OIEN, I. & FALLANG, B. 2008. Goal-oriented rehabilitation of preschoolers with cerebral palsy--a multi-case study of combined use of the Canadian Occupational Performance Measure (COPM) and the Goal Attainment Scaling (GAS). *Dev Neurorehabil*, 11, 252-9.
- OSTOJIC, K., PAGET, S. P. & MORROW, A. M. 2019. Management of pain in children and adolescents with cerebral palsy: a systematic review. *Developmental Medicine and Child Neurology*, 61, 315-+.
- OTERO, S. C., EISER, C., WRIGHT, N. P. & BUTLER, G. 2013. Implications of parent and child quality of life assessments for decisions about growth hormone treatment in eligible children. *Child Care Health Dev*, 39, 782-8.
- OULTON, K., OLDRIEVE, N., BAYLISS, J., JONES, V., MANNING, I., SHIPWAY, L. & GIBSON, F. 2017. *Using participatory and creative research methods to develop and pilot an informative game for preparing children for blood tests.*
- PAGET, S., M SWINNEY, C., L O BURTON, K., BAU, K. & J O'FLAHERTY, S. 2018a. *Systemic adverse events after botulinum neurotoxin A injections in children with cerebral palsy.*
- PAGET, S. P., SWINNEY, C. M., BURTON, K. L. O., BAU, K. & O'FLAHERTY, S. J. 2018b. Systemic adverse events after botulinum neurotoxin A injections in children with cerebral palsy. *Developmental Medicine & Child Neurology*, 60, 1172-1177.
- PALISANO, R., ROSENBAUM, P., WALTER, S., RUSSELL, D., WOOD, E. & GALUPPI, B. 1997. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*, 39, 214-23.
- PALISANO, R. J. 2006. A collaborative model of service delivery for children with movement disorders: A framework for evidence-based decision making. *Physical Therapy*, 86, 1295-1305.
- PALISANO, R. J., CHIARELLO, L. A., KING, G. A., NOVAK, I., STONER, T. & FISS, A. 2012. Participation-based therapy for children with physical disabilities. *Disabil Rehabil*, 34, 1041-52.

- PALISANO, R. J., DI REZZE, B., STEWART, D., ROSENBAUM, P. L., HLYVA, O., FREEMAN, M., NGUYEN, T. & GORTER, J. W. 2017. Life course health development of individuals with neurodevelopmental conditions. *Developmental Medicine & Child Neurology*, 59, 470-476.
- PAOLICELLI, P. B., FERRARI, A., LODESANI, M., MUZZINI, S., SASSI, S., MAORET, A., BIANCHINI, E. & CIONI, G. 2001. Use of botulinum toxin type A in walking disorders of children with cerebral palsy. *Europa Medicophysica*, 37, 83-92.
- PAPAVASILIOU, A. S., NIKAINA, I., FOSKA, K., BOUROS, P., MITSOU, G. & FILIOPOULOS, C. 2013. Safety of botulinum toxin A in children and adolescents with cerebral palsy in a pragmatic setting. *Toxins (Basel)*, 5, 524-36.
- PAPAVASILIOU, A. S., RAPIDI, C. A., FILIOPOULOS, C., RIZOU, C. & SKOUTELI, H. N. 2006. Evaluation of a multimodal management of prematurity-related spasticity. *Pediatric Neurology*, 35, 400-7.
- PARK, E. S., PARK, C. I., KIM, D. Y. & KIM, Y. R. 2002. The effect of spasticity on cortical somatosensory-evoked potentials: changes of cortical somatosensory-evoked potentials after botulinum toxin type A injection. *Archives of Physical Medicine & Rehabilitation*, 83, 1592-6.
- PARK, E. S., SIM, E., RHA, D. W. & JUNG, S. 2014. Architectural changes of the gastrocnemius muscle after botulinum toxin type A injection in children with cerebral palsy. *Yonsei Medical Journal*, 55, 1406-12.
- PARK, J. & PARK, H. J. 2017. Botulinum Toxin for the Treatment of Neuropathic Pain. *Toxins*, 9, 260.
- PARKINSON, K. N., GIBSON, L., DICKINSON, H. O. & COLVER, A. F. 2010. Pain in children with cerebral palsy: a cross-sectional multicentre European study. *Acta Paediatr*, 99, 446-51.
- PENNINGTON, M., SUMMERS, J., COKER, B., EDDY, S., KARTHA, M. R., EDWARDS, K., FREEMAN, R., GOODDEN, J., POWELL, H., VERITY, C. & PEACOCK, J. L. 2020. Selective dorsal rhizotomy; evidence on cost-effectiveness from England. *PLOS ONE*, 15, e0236783.
- PEPLOW, U. C. & CARPENTER, C. 2013. Perceptions of Parents of Children with Cerebral Palsy About the Relevance of, and Adherence to, Exercise Programs: A Qualitative Study. *Physical & Occupational Therapy In Pediatrics*, 33, 285-299.
- PERSSON, E., RIVANO-FISCHER, M. & EKLUND, M. 2004. Evaluation of changes in occupational performance among patients in a pain management program. *J Rehabil Med*, 36, 85-91.
- PINGEL, J., WIENECKE, J., LORENTZEN, J. & NIELSEN, J. B. 2016. Botulinum toxin injection causes hyper-reflexia and increased muscle stiffness of the triceps surae muscle in the rat. *Journal of Neurophysiology*, 116, 2615-2623.
- POPE, C. & MAYS, N. 1995. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ*, 311, 42-45.
- PRESTON, N., CLARKE, M. & BHAKTA, B. 2011. Development of a framework to define the functional goals and outcomes of botulinum toxin A spasticity treatment relevant to the child and family living with cerebral palsy using the International Classification of Functioning, Disability and Health for Children and Youth. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine*, 43, 1010-1015.
- R CORE TEAM 2021. R: A language and environment for statistical computing. . In: COMPUTING, R. F. F. S. (ed.). Vienna, Austria.
- RASETTI-ESCARGUEIL, C., LEMICHEZ, E. & POPOFF, M. R. 2018. Variability of Botulinum Toxins: Challenges and Opportunities for the Future. *Toxins (Basel)*, 10.

- READ, F. A., BOYD, R. N. & BARBER, L. A. 2016. Longitudinal assessment of gait quality in children with diplegia following serial lower limb intramuscular Botulinum Toxin-A injections. *Developmental Medicine and Child Neurology*, 58, 19.
- READ, F. A., BOYD, R. N. & BARBER, L. A. 2017. Longitudinal assessment of gait quality in children with bilateral cerebral palsy following repeated lower limb intramuscular Botulinum toxin-A injections. *Research in Developmental Disabilities*, 68, 35-41.
- REEDMAN, S., BOYD, R. N. & SAKZEWSKI, L. 2017. The efficacy of interventions to increase physical activity participation of children with cerebral palsy: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology*, 59, 1011-1018.
- REEDMAN, S. E., BOYD, R. N., TROST, S. G., ELLIOTT, C. & SAKZEWSKI, L. 2019. Efficacy of Participation-Focused Therapy on Performance of Physical Activity Participation Goals and Habitual Physical Activity in Children With Cerebral Palsy: A Randomized Controlled Trial. *Arch Phys Med Rehabil*, 100, 676-686.
- REES, C. 2011. *Introduction to Research for Midwives*, London, Churchill Livingstone.
- REID, S. M., CARLIN, J. B. & REDDIHOUGH, D. S. 2011. Using the Gross Motor Function Classification System to describe patterns of motor severity in cerebral palsy. *Dev Med Child Neurol*, 53, 1007-12.
- ROBERTS, B. W., WALTON, K. E. & VIECHTBAUER, W. 2006. Patterns of mean-level change in personality traits across the life course: A meta-analysis of longitudinal studies. *Psychological Bulletin*, 132, 1-25.
- ROEBROECK, M. E., JAHNSEN, R., CARONA, C., KENT, R. M. & CHAMBERLAIN, M. A. 2009. Adult outcomes and lifespan issues for people with childhood-onset physical disability. *Dev Med Child Neurol*, 51, 670-8.
- ROQUET, M., GARLANTEZEC, R., GALLIEN, P., PONS, C., HOUX, L., REMY-NERIS, O. & BROCHARD, S. 2016. From childhood to adulthood: Care management for individuals with cerebral palsy. *Developmental Medicine and Child Neurology*, 58, 21-22.
- ROSE, G. E., LIGHTBODY, K. A., FERGUSON, R. G., WALSH, J. C. & ROBB, J. E. 2010. Natural history of flexed knee gait in diplegic cerebral palsy evaluated by gait analysis in children who have not had surgery. *Gait Posture*, 31, 351-4.
- ROSENBAUM, P. 2003. Controversial treatment of spasticity: exploring alternative therapies for motor function in children with cerebral palsy. *J Child Neurol*, 18 Suppl 1, S89-94.
- ROSENBAUM, P. 2020. How do we know if interventions in developmental disability are effective? *Developmental Medicine & Child Neurology*, 62, 1344-1344.
- ROSENBAUM, P. 2021a. Challenges of Guidelines: A Look at the Systematic Review of Clinical Guidelines Related to the Care of Individuals With Cerebral Palsy. *Arch Phys Med Rehabil*, 102, 796-798.
- ROSENBAUM, P. 2021b. Developmental Disability: Families and Functioning in Child and Adolescence. *Frontiers in Rehabilitation Sciences*, 2.
- ROSENBAUM, P. & GORTER, J. W. 2012. The 'F-words' in childhood disability: I swear this is how we should think! *Child Care Health Dev*, 38, 457-63.
- ROSENBAUM, P. & STEWART, D. 2004. The World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. *Semin Pediatr Neurol*, 11, 5-10.
- ROSENBAUM, P. L., WALTER, S. D., HANNA, S. E., PALISANO, R. J., RUSSELL, D. J., RAINA, P., WOOD, E., BARTLETT, D. J. & GALUPPI, B. E. 2002. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. *Jama*, 288, 1357-63.
- ROZKALNE, Z. & BERTULE, D. 2014. Measurement of activities and participation for children with cerebral palsy: A systematic review. *SHS Web of Conferences*, 10, 00038.

- RSTUDIO TEAM 2021. Integrated Development Environment for R. . In: RSTUDIO, P. (ed.). Boston, MA
- RUSSELL, D. J., AVERY, L. M., ROSENBAUM, P. L., RAINA, P. S., WALTER, S. D. & PALISANO, R. J. 2000. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity. *Phys Ther*, 80, 873-85.
- RYLL, U., BASTIAENEN, C., BIE, R. & STAAL, B. 2011a. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review (Provisional abstract). *Developmental Medicine and Child Neurology* [Online], 53. Available: <http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011001565/frame.html>.
- RYLL, U., BASTIAENEN, C., R, D. E. B. & STAAL, B. 2011b. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology*, 53, 210-216.
- SACKETT, D. L. 1997. Evidence-based medicine. *Semin Perinatol*, 21, 3-5.
- SAKZEWSKI, L., BOYD, R. & ZIVIANI, J. 2007. Clinimetric properties of participation measures for 5- to 13-year-old children with cerebral palsy: a systematic review. *Dev Med Child Neurol*, 49, 232-40.
- SAKZEWSKI, L., ZIVIANI, J., ABBOTT, D. F., MACDONELL, R. A., JACKSON, G. D. & BOYD, R. N. 2011. Participation outcomes in a randomized trial of 2 models of upper-limb rehabilitation for children with congenital hemiplegia. *Arch Phys Med Rehabil*, 92, 531-9.
- SANGER, T. D., DELGADO, M. R., GAEBLER-SPIRA, D., HALLETT, M. & MINK, J. W. 2003. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics*, 111, e89-97.
- SATILA, H., PIETIKAINEN, T., IISALO, T., LEHTONEN-RATY, P., SALO, M., HAATAJA, R., KOIVIKKO, M. & AUTTI-RAMO, I. 2008. Botulinum toxin type A injections into the calf muscles for treatment of spastic equinus in cerebral palsy: A randomized trial comparing single and multiple injection sites. *American Journal of Physical Medicine and Rehabilitation*, 87, 386-394.
- SAWYER, M. G., BITTMAN, M., AM, L. A. G., CRETENDEN, A. D., BOROJEVIC, N., RAGHAVENDRA, P. & RUSSO, R. 2011. Time demands of caring for children with cerebral palsy: what are the implications for maternal mental health? *Dev Med Child Neurol*, 53, 338-43.
- SCHASFOORT, F., PANGALILA, R., SNEEKES, E. M., CATSMAN, C., BECHER, J., HOREMANS, H., STAM, H. J., DALLMEIJER, A. J. & BUSSMANN, J. B. J. 2018. Intramuscular botulinum toxin prior to comprehensive rehabilitation has no added value for improving motor impairments, gait kinematics and goal attainment in walking children with spastic cerebral palsy. *Journal of Rehabilitation Medicine*, 50, 732-742.
- SCHASFOORT, F. C., PANGALILA, R. F., DALLMEIJER, A. J., CATSMAN, C. E., SNEEKES, E. M., ELINE, E., STAM, H. J., BECHER, J. G. & BUSSMANN, J. B. J. 2017. Evaluation of the added value of botulinum toxin treatment and intensive physiotherapy to improve body function and structure in children with spastic cerebral palsy. *Developmental Medicine and Child Neurology*, 59 (Supplement 2), 21.
- SCHLESS, S. H., CENNI, F., BAR-ON, L., HANSEN, B., KALKMAN, B., O'BRIEN, T., AERTBELIEN, E., VAN CAMPENHOUT, A., MOLENAERS, G. & DESLOOVERE, K. 2018. Medial gastrocnemius volume and echo-intensity after botulinum neurotoxin A interventions in children with spastic cerebral palsy. *Developmental Medicine and Child Neurology*.
- SCHOLTES, V. A., BECHER, J. G., JANSSEN-POTTEN, Y. J., DEKKERS, H., SMALLENBROEK, L. & DALLMEIJER, A. J. 2012. Effectiveness of functional progressive resistance exercise

- training on walking ability in children with cerebral palsy: a randomized controlled trial. *Res Dev Disabil*, 33.
- SCHROEDER, A. S., ERTL-WAGNER, B., BRITSCH, S., SCHRODER, J. M., NIKOLIN, S., WEIS, J., MULLER-FELBER, W., KOERTE, I., STEHR, M., BERWECK, S., BORGGRAEFE, I. & HEINEN, F. 2009a. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. *Mov Disord*, 24, 1494-503.
- SCHROEDER, S. A., SCHRODER, M., ERTL-WAGNER, B., BERWECK, S., MUELLER-FELBER, W. & HEINEN, F. 2009b. The time course of botulinum toxin type a within the muscle - In vivo two year follow-up using MRI, ultrasound, and EMG substantiated by muscle histopathology. *Developmental Medicine and Child Neurology*, 51, 55.
- SCOTT, A., KENNEDY, R. & STUBBS, H. 1985. *Botulinum A Toxin Injection as a Treatment for Blepharospasm*.
- SHEVELL, M., OSKOUJ, M., WOOD, E., KIRTON, A., VAN RENSBURG, E., BUCKLEY, D., NG, P. & MAJNEMER, A. 2019. Family-centred health care for children with cerebral palsy. *Developmental Medicine & Child Neurology*, 61, 62-68.
- SHIKAKO-THOMAS, K., MAJNEMER, A., LAW, M. & LACH, L. 2008. Determinants of participation in leisure activities in children and youth with cerebral palsy: systematic review. *Phys Occup Ther Pediatr*, 28, 155-69.
- SHIMMELL, L. J., GORTER, J. W., JACKSON, D., WRIGHT, M. & GALUPPI, B. 2013. "It's the participation that motivates him": physical activity experiences of youth with cerebral palsy and their parents. *Phys Occup Ther Pediatr*, 33, 405-20.
- SHORE BENJAMIN, NATHAN, W. & H., K. G. 2010. Surgical correction of equinus deformity in children with cerebral palsy: a systematic review. *Journal of Children's Orthopaedics*, 4, 277-290.
- SHORTLAND, A. 2009. Muscle deficits in cerebral palsy and early loss of mobility: can we learn something from our elders? *Developmental Medicine & Child Neurology*, 51, 59-63.
- SHORTLAND, A., FAIRHURST, C. F., GOUGH, M. & FORSTER, T. 2013. The effect of Botulinum toxin on muscle volume in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 55, 36.
- SHROUT, P. E. & FLEISS, J., L. 1979. Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*, 86, 420-428.
- SIM, E., PARK, E. & JUNG, S. 2012. Architectural change of gastrocnemius muscle after botulinum toxin injection in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 54, 20-21.
- SMITS, D.-W., GORTER, J. W., HANNA, S. E., DALLMEIJER, A. J., VAN ECK, M., ROEBROECK, M. E., VOS, R. C., KETELAAR, M. & GROUP, O. B. O. T. P. P. S. 2013. Longitudinal development of gross motor function among Dutch children and young adults with cerebral palsy: an investigation of motor growth curves. *Developmental Medicine & Child Neurology*, 55, 378-384.
- SMITS, D.-W., GORTER, J. W., KETELAAR, M., VAN SCHIE, P. E., DALLMEIJER, A. J., LINDEMAN, E. & JONGMANS, M. J. 2010. Relationship between gross motor capacity and daily-life mobility in children with cerebral palsy. *Developmental Medicine & Child Neurology*, 52, e60-e66.
- SRINIVASAN, R., KULKARNI, V., SMRITI, S., TEPLICKY, R. & ANABY, D. 2021. Cross-Cultural Adaptation and Evaluation of the Participation and Environment Measure for Children and Youth to the Indian Context-A Mixed-Methods Study. *Int J Environ Res Public Health*, 18.
- STÅLBERG, A., SANDBERG, A., SÖDERBÄCK, M. & LARSSON, T. 2016. The child's perspective as a guiding principle: Young children as co-designers in the design of an interactive

- application meant to facilitate participation in healthcare situations. *Journal of Biomedical Informatics*, 61, 149-158.
- STEENBERGEN, B. 2014. Movement quality: is beauty only in the eyes of the beholder? *Developmental Medicine & Child Neurology*, 56, 709-710.
- STEVENSON, K., JACK, S., O'MARA, L. & LEGRIS, J. 2015. Registered nurses' experiences of patient violence on acute care psychiatric inpatient units: An interpretive descriptive study. *BMC Nursing*, 14.
- STRATFORD, P. W. & RIDDLE, D. L. 2013. Assessing the amount of change in an outcome measure is not the same as assessing the importance of change. *Physiotherapy Canada. Physiotherapie Canada*, 65, 244-247.
- STROBL, W., THEOLOGIS, T., BRUNNER, R., KOCER, S., VIEHWEGER, E., PASCUAL-PASCUAL, I. & PLACZEK, R. 2015. Best Clinical Practice in Botulinum Toxin Treatment for Children with Cerebral Palsy. *Toxins*, 7, 1629-1648.
- SUMMERS, J., COKER B, EDDY S, ELSTAD M, BUNCE C, BOURMPAKI E, PENNINGTON M, AQUILINA K, CAWKER S, EDWARDS R, GOODDEN J, HAWES S, MCCUNE K, PETTORINI B, SMITH J, SNEADE C, VLOEBERGHES M, PATRICK H, POWELL H, V., ERITY C & JL, P. 2019. Selective dorsal rhizotomy in ambulant children with cerebral palsy: an observational cohort study. *Lancet Child Adolesc Health*, 3, 455-462.
- SUNG, K. H., CHUNG, C. Y., LEE, K. M., LEE, Y. K., LEE, S. Y., LEE, J., CHOI, I. H., CHO, T. J., YOO, W. J. & PARK, M. S. 2013. Conflict of Interest in the Assessment of Botulinum Toxin A Injections in Patients With Cerebral Palsy: A Systematic Review. *Journal of Pediatric Orthopaedics*, 33, 494-500.
- SUTHERLAND, E., HILL, B., SINGER, B. J., ASHFORD, S., HOARE, B., HASTINGS-ISON, T., FHEODOROFF, K., BERWICK, S., DOBSON, F. & WILLIAMS, G. 2022. Do randomised controlled trials evaluating functional outcomes following botulinum neurotoxin-A align with focal spasticity guidelines? A systematic review. *Disabil Rehabil*, 1-9.
- SVEHLIK, M., KRAUS, T., STEINWENDER, G., ZWICK, E. B., LADECKY, M., SZABO, Z. & LINHART, W. E. 2012. Repeated multilevel botulinum toxin A treatment maintains long-term walking ability in children with cerebral palsy. *Ceska a Slovenska Neurologie a Neurochirurgie*, 75, 737-741.
- TEDDLIE, C. & TASHAKKORI, A. 2011. Mixed methods research. *The Sage handbook of qualitative research*, 4, 285-300.
- TEDROFF, K. 2009. Short and long term effects of Botulinum toxin A in children. *Developmental Medicine and Child Neurology*, 51, 10.
- TEDROFF, K., LOWING, K., HAGLUND-AKERLIND, Y. & FORSSBERG, H. 2009. Does Botulinum toxin-A treatment from an early age facilitate normal gait development, decrease contracture development and improve 'daily life' in children with cerebral palsy? A randomised controlled trial. *Developmental Medicine and Child Neurology*, 51, 8-9.
- TEDROFF, K., LOWING, K., HAGLUND-AKERLIND, Y., GUTIERREZ-FAREWIK, E. & FORSSBERG, H. 2010. Botulinum toxin A treatment in toddlers with cerebral palsy. *Acta Paediatrica*, 99, 1156-62.
- THOMAS, R., JOHNSTON, L., SAKZEWSKI, L., KENTISH, M. & BOYD, R. 2016. Evaluation of group versus individual physiotherapy following lower limb intra-muscular Botulinum Toxin-Type A injections for ambulant children with cerebral palsy: a single-blind randomized comparison trial. *Research in developmental disabilities*, 53-54, 267-278.
- THOMASON, P., TAN, A., DONNAN, A., RODDA, J., GRAHAM, H. K. & NARAYANAN, U. 2018. The Gait Outcomes Assessment List (GOAL): validation of a new assessment of gait function for children with cerebral palsy. *Developmental Medicine & Child Neurology*, 60, 618-623.

- THOMPSON BURDINE, J., THORNE, S. & SANDHU, G. 2021. Interpretive description: A flexible qualitative methodology for medical education research. *Medical Education*, 55, 336-343.
- THOMPSON, N. S., BAKER, R. J., COSGROVE, A. P., CORRY, I. S. & GRAHAM, H. K. 1998. Musculoskeletal modelling in determining the effect of botulinum toxin on the hamstrings of patients with crouch gait. *Developmental Medicine & Child Neurology*, 40, 622-5.
- THORNE, S. 2016. *Interpretive Description: Qualitative Research for Applied Practice*, New York, Routledge.
- TILTON, A., MACIAG-TYMECKA, I., JOZWIAK, M., UNLU, E., VELEZ, J., TSE, A. & PICAUT, P. 2015. Baseline characteristics of patients from a phase 3 program to assess abobotulinumtoxinA (Dysport) in the treatment of spasticity and functional impairments in children with dynamic equinus foot deformity due to cerebral palsy. *Toxicon*, 93, S59-S60.
- TILTON, A., RUSSMAN, B., AYDIN, R., DINCER, U., ESCOBAR, R. G., KUTLAY, S., LIPCZYK, Z., VELEZ, J. C., GRANDOULIER, A. S., TSE, A., PICAUT, P. & DELGADO, M. R. 2017. AbobotulinumtoxinA (Dysport) improves function according to goal attainment in children with dynamic equinus due to cerebral palsy. *Journal of Child Neurology*, 32, 482-487.
- TIMANS, R., WOUTERS, P. & HEILBRON, J. 2019. Mixed methods research: what it is and what it could be. *Theory and Society*, 48, 193-216.
- TSE, A., TILTON, A., BONIKOWSKI, M., CARRANZA, J., DURSUN, N., PICAUT, P. & DELGADO, M. R. 2014. Goal selection using the Goal Attainment Scale in ambulatory patients with cerebral palsy according to GMFSC levels in a randomized, double-blind placebo-controlled study of abobotulinumtoxinA (Dysport). *Developmental Medicine and Child Neurology*, 56, 11.
- TSZE, D. S., HIRSCHFELD, G., VON BAEYER, C. L., BULLOCH, B. & DAYAN, P. S. 2015. Clinically significant differences in acute pain measured on self-report pain scales in children. *Acad Emerg Med*, 22, 415-22.
- TUSTIN, K., GIMENO, H., MORTON, E. & MARSDEN, J. 2016. Rater reliability and scoring duration of the Quality Function Measure in ambulant children with hyperkinetic movement disorders. *Dev Med Child Neurol*, 58, 822-8.
- VALENTINE, J., DAVIDSON, S.-A., BEAR, N., BLAIR, E., PATERSON, L., WARD, R., FORBES, D. & ELLIOTT, C. 2020a. A prospective study investigating gross motor function of children with cerebral palsy and GMFCS level II after long-term Botulinum toxin type A use. *BMC pediatrics*, 20, 7-7.
- VALENTINE, J., DAVIDSON, S.-A., BEAR, N., BLAIR, E., WARD, R., THORNTON, A., STANNAGE, K., WATSON, L., FORBES, D. & ELLIOTT, C. 2021. Botulinum toxin and surgical intervention in children and adolescents with cerebral palsy: who, when and why do we treat? *Disability and Rehabilitation*, 43, 936-943.
- VALENTINE, J., DAVIDSON, S. A., BEAR, N., BLAIR, E., PATERSON, L., WARD, R., FORBES, D. & ELLIOTT, C. 2020b. A prospective study investigating gross motor function of children with cerebral palsy and GMFCS level II after long-term Botulinum toxin type A use. *Bmc Pediatrics*, 20.
- VALENTINE, J., STANNAGE, K., FABIAN, V., ELLIS, K., REID, S., PITCHER, C. & ELLIOTT, C. 2016. Muscle histopathology in children with spastic cerebral palsy receiving botulinum toxin type A. *Muscle and Nerve*, 53, 407-414.
- VAN CAMPENHOUT, A., VERHAEGEN, A., PANS, S. & MOLENAERS, G. 2013. Botulinum toxin type A injections in the psoas muscle of children with cerebral palsy: Muscle atrophy after motor end plate-targeted injections. *Research in Developmental Disabilities*, 34, 1052-1058.

- VERKERK, G. J. Q., VAN DER MOLEN-MEULMEESTER, L. & ALSEM, M. W. 2021. How children and their parents value using the Canadian Occupational Performance Measure (COPM) with children themselves. *Journal of pediatric rehabilitation medicine*, 14, 7-17.
- VERSCHUREN, O., SMORENBURG, A. R. P., LUIKING, Y., BELL, K., BARBER, L. & PETERSON, M. D. 2018. Determinants of muscle preservation in individuals with cerebral palsy across the lifespan: a narrative review of the literature. *J Cachexia Sarcopenia Muscle*, 9, 453-464.
- VILLALBA, F. J., POLICASTRO, P. O., SOLIÑO, S., ANDREU, M., NOVOA, G. A., RAGUZZI, I. A. & PIEROBON, A. 2021. Standard measurement error and minimal detectable change of the Back-PAQ ArgSpan questionnaire: Secondary analysis. *Musculoskeletal Science & Practice*, 51.
- VYSLYSEL, G., BARKER, D. & HUBBARD, I. J. 2021. The Canadian Occupational Performance Measure (COPM) as Routine Practice in Community-Based Rehabilitation: A Retrospective Chart Review. *Archives of rehabilitation research and clinical translation*, 3, 100134-100134.
- WALKER, B. A., HOKE, K., MANLEY, M., FLYNN, S. & JOHNSON, R. 2018. Establishing the Reliability and Validity of Health in Motion Automated Falls Screening Tool. *Advances in Aging Research*, Vol.07 No.03, 12.
- WALLEN, M., O'FLAHERTY, S. & WAUGH, M. 2007. Functional outcomes of intramuscular botulinum toxin type a and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial. *Archives of physical medicine and rehabilitation* [Online], 88. Available: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/864/CN-00574864/frame.html>.
- WANG, H.-Y. & YANG, Y. H. 2006. Evaluating the Responsiveness of 2 Versions of the Gross Motor Function Measure for Children With Cerebral Palsy. *Archives of Physical Medicine and Rehabilitation*, 87, 51-56.
- WARD, A. B., MOLENAERS, G., COLOSIMO, C. & BERARDELLI, A. 2006. Clinical value of botulinum toxin in neurological indications. *European Journal of Neurology*, 13 Suppl 4, 20-6.
- WATERS, E., DAVIS, E., BOYD, R., REDDIHOUGH, D., MACKINNON, A., GRAHAM, H. K., WOLFE, R., STEVENSON, R., BJORNSON, K. & BLAIR, E. 2006. *Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-child) Primary Caregiver Questionnaire (4–12 years)*, Melbourne, Deakin University.
- WATERS, E., DAVIS, E., MACKINNON, A., BOYD, R., GRAHAM, H. K., KAI LO, S., WOLFE, R., STEVENSON, R., BJORNSON, K. & BLAIR, E. 2007. Psychometric properties of the quality of life questionnaire for children with CP. *Dev Med Child Neurol*, 49.
- WEAVER, J., COGAN, A., DAVIDSON, L., SCHLUMPF, K. & MALLINSON, T. 2020. When is Change Meaningful?: A Comparison of the MCID, MDC, and cMDC. *Archives of Physical Medicine and Rehabilitation*, 101, e57.
- WEIGL, D. M., ARBEL, N., KATZ, K., BECKER, T. & BAR-ON, E. 2007. Botulinum toxin for the treatment of spasticity in children: attainment of treatment goals. *Journal of Pediatric Orthopaedics, Part B*, 16, 293-6.
- WHO 2007. International Classification of Functioning, Disability and Health – Children and Youth Version (ICF-CY). *Geneva: World Health Organization*.
- WIART, L., KOLASKI, K., BUTLER, C., VOGTLE, L., LOGAN, L. R., HICKMAN, R., ROMEISER, J., SAMSON-FANG, L., MATSUBA, C. A., BAIRD, M. W., ROXBOROUGH, L., MAYSON, T. & DINU, I. 2012. Interrater reliability and convergent validity of the American Academy for Cerebral Palsy and Developmental Medicine methodology for conducting systematic reviews. *Developmental Medicine & Child Neurology*, 54, 606-611.

- WILLIAMS, E. N., CARROLL, S. G., REDDIHOUGH, D. S., PHILLIPS, B. A. & GALEA, M. P. 2005. Investigation of the timed 'up & go' test in children. *Dev Med Child Neurol*, 47, 518-24.
- WILLIAMS, S., ELLIOTT, C., GUBBAY, A., SPITS, M. & VALENTINE, J. 2012. The immediate effect of Botulinum Toxin Type-A on muscle morphology and strength in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 54, 35-36.
- WILLIAMS, S. A., ELLIOTT, C., VALENTINE, J., GUBBAY, A., SHIPMAN, P. & REID, S. 2013a. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength. *Disability & Rehabilitation*, 35, 596-605.
- WILLIAMS, S. A., REID, S., ELLIOTT, C., SHIPMAN, P. & VALENTINE, J. 2013b. Muscle volume alterations in spastic muscles immediately following botulinum toxin type-A treatment in children with cerebral palsy. *Developmental Medicine and Child Neurology*, 55, 813-820.
- WILLIAMS, S. A., REID, S., VALENTINE, J., SHILLINGTON, T. & ELLIOTT, C. 2014. Activity, participation and quality of life in children with cerebral palsy: Can a combined approach of strength training and botulinum neurotoxin type-A help? *Developmental Medicine and Child Neurology*, 56, 76.
- WISSEL, J., MULLER, J., BALDAUF, A., UNG, S. C., NDAYISABA, J. P., STOCKL, B., FRISCHHUT, B., HABERFELLNER, H. & POEWE, W. 1999. Gait analysis to assess the effects of botulinum toxin type A treatment in cerebral palsy: An open-label study in 10 children with equinus gait pattern. *European Journal of Neurology*, 6, S63-S67.
- WONG, A. M., PEI, Y. C., LUI, T. N., CHEN, C. L., WANG, C. M. & CHUNG, C. Y. 2005. Comparison between botulinum toxin type A injection and selective posterior rhizotomy in improving gait performance in children with cerebral palsy. *Journal of neurosurgery*, 102, 385-389.
- WONG, C., WESTPHALL, I. & MICHELSEN, J. S. 2022. Measuring Effects on Pain and Quality of Life after Abobotulinum Toxin A Injections in Children with Cerebral Palsy. *Toxins*, 14, 43.
- WOOD, E. & ROSENBAUM, P. 2000. The gross motor function classification system for cerebral palsy: a study of reliability and stability over time. *Dev Med Child Neurol*, 42, 292-6.
- WRIGHT, E. 2016. Evaluation of movement quality: a new tool for children with hyperkinetic movement disorders. *Developmental Medicine & Child Neurology*, 58, 789-790.
- WRIGHT, F. V., ROSENBAUM, P., FEHLINGS, D., MESTERMAN, R., BREUER, U. & KIM, M. 2014a. The Quality Function Measure: reliability and discriminant validity of a new measure of quality of gross motor movement in ambulatory children with cerebral palsy. *Dev Med Child Neurol*, 56, 770-8.
- WRIGHT, F. V., ROSENBAUM, P. L., GOLDSMITH, C. H., LAW, M. & FEHLINGS, D. L. 2008. How do changes in body functions and structures, activity, and participation relate in children with cerebral palsy? *Developmental Medicine & Child Neurology*, 50, 283-9.
- WRIGHT, V., BREUER, U. & PATRICK, L. 2014b. Quality FM Detailed Scoring Guidelines. In: BLOORVIEW RESEARCH INSTITUTE, T., CANADA (ed.).
- WU, Y. P., DEATRICK, J. A., MCQUAID, E. L. & THOMPSON, D. 2019. A Primer on Mixed Methods for Pediatric Researchers. *Journal of Pediatric Psychology*, 44, 905-913.
- XU, K. S., YAN, T. B. & MAI, J. N. 2006. Effects of botulinum toxin guided by electric stimulation on spasticity in ankle plantar flexor of children with cerebral palsy: a randomized trial. [Chinese]. *Zhonghua er ke za zhi*, Chinese journal of pediatrics. 44, 913-917.

- YAP, R., MAJNEMER, A., BENAROCH, T. & CANTIN, M. A. 2010. Determinants of responsiveness to botulinum toxin, casting, and bracing in the treatment of spastic equinus in children with cerebral palsy. *Developmental Medicine & Child Neurology*, 52, 186-93.
- ZHU, D., WANG, M., WANG, J., ZHANG, W., LI, H., YANG, P., XIONG, H., NIU, G., LI, S. & ZHAO, Y. 2016. [Effect of botulinum toxin A injection in the treatment of gastrocnemius spasticity in children aged 9-36 months with cerebral palsy: a prospective study]. *Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics* [Online], 18. Available: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/191/CN-01168191/frame.html>.
- ZOELLNER, J. & HARRIS, J. E. 2017. Mixed-Methods Research in Nutrition and Dietetics. *Journal of the Academy of Nutrition and Dietetics*, 117, 683-697.

Chapter 14 Appendices

14.1 Ethical Approval

GOSH Data Storage Policy



General Data Protection Regulation and Research - Privacy Notice
Version : 4
Authored by: Thomas Lewis and Natassa Spiridou
Approved by: Head of Information Governance and
Head of Research Governance (based on guidance from HRA)
Effective Date: November 2018

The General Data Protection Regulation (GDPR) comes into force on 25th May 2018 which is designed to enable individuals to better control their personal data. The Health Research Authority (HRA) has published guidance about research and the general use of patient information which can be found at [HRA patient information](#).

As a NHS organisation we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. In any case all research, using identifiable or non-identifiable data, would have to go through a governance process and may require approval by a Research Ethics Committee.

As a research hospital, GOSH is at the forefront of using innovative technologies in the clinical treatment of patients and in support of pioneering research to find cures of complex and rare conditions. We have set-up the Digital Research Environment (DRE), which is a research and innovation platform within GOSH. The DRE provides routinely collected clinical and other data for use in approved research studies or clinical audits to improve patient health, care and services. Only de-identified/anonymised data are made available to researchers via the DRE. Any published research results will only include de-identified/anonymised data.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will be used for the purpose of health and social care research, or to contact you about future opportunities to participate in research.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the [UK Policy Framework for Health and Social Care Research](#).

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

Our Data Protection Officer can be contacted at your.data@gosh.nhs.uk

HRA Approval



Health Research Authority

Ms Lesley Katchburian
Clinical Specialist Physiotherapist /NIHR Doctoral Fellow
Great Ormond Street NHS FT
Great Ormond St,
London
WC1N 3JH

Email: hra.approval@nhs.net

29 June 2017

Dear Ms Katchburian,

Letter of HRA Approval

Study title: Understanding Clinical and Patient Reported Response of Children and Young People with Cerebral Palsy to Botulinum Toxin A: a Longitudinal Observational Study

IRAS project ID: 211617

REC reference: 17/LO/0579

Sponsor UCL Great Ormond Street Institute of child health

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](http://www.hra.nhs.uk), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](http://www.hra.nhs.uk).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

Your IRAS project ID is **211617**. Please quote this on all correspondence.

Yours sincerely

[REDACTED]

Senior Assessor

Email: hra.approval@nhs.net

Copy to: [REDACTED] *Greater Ormond Street Hospital*
[REDACTED] *Great Ormond Street Hospital for children NHS FT,*

*Personal details removed to maintain privacy

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity Certificate UCL]		
GP/consultant information sheets or letters [Letter to Local GP]	1	12 April 2017
GP/consultant information sheets or letters [Letter to Local Physiotherapist]	1	21 February 2017
Interview schedules or topic guides for participants [Phase II Interview Schedule for Parent/Carer]	1	21 February 2017
Interview schedules or topic guides for participants [Phase II Interview Schedule for CYP]	1	21 February 2017
IRAS Application Form [IRAS_Form_16032017]		16 March 2017
IRAS Application Form XML file [IRAS_Form_16032017]		16 March 2017
IRAS Checklist XML [Checklist_08052017]		08 May 2017
Letter from funder [NIHR/HEE Clinical Doctoral Research Fellowship]		
Letters of invitation to participant [Phase I Motor Disorders Clinic Invitation Letter]	1	21 February 2017
Letters of invitation to participant [Phase I Invitation to Parents by Post]	1	21 February 2017
Letters of invitation to participant [Phase II Invitation to Parents]	1	21 February 2017
Other [Confirmation of data retention]		18 May 2017
Participant consent form [Phase I Assent words only (13-18 years)]	3	08 May 2017
Participant consent form [Phase I Consent for Parent/Carer]	2	12 April 2017
Participant consent form [Phase I Consent for Parent/Carer for Child]	2	12 April 2017
Participant consent form [Phase II Consent for Parent/Carer]	1	21 February 2017
Participant consent form [Phase II Consent for Parent/Carer for Child]	1	21 February 2017
Participant consent form [Phase II Assent words only (13-18 years)]	1	21 February 2017
Participant consent form [Phase I Assent words and pictures (9-12 years)]	1	21 February 2017
Participant consent form [Phase II Assent words and pictures (9-12 years)]	1	21 February 2017
Participant consent form [Phase I Assent Symbols and Words (4- 8 years)]	1	21 February 2017
Participant consent form [Phase II Assent Symbols and Words (4- 8 years)]	1	21 February 2017
Participant consent form [Phase I Assent symbols only (communication difficulties)]	1	21 February 2017
Participant consent form [Phase II Assent symbols only (communication difficulties)]	1	21 February 2017
Participant information sheet (PIS) [Phase II PIS Symbols only (communication difficulties)]	1	21 February 2017
Participant information sheet (PIS) [Phase I Parent/Carer PIS]	1	21 February 2017
Participant information sheet (PIS) [Phase II Parent/Carer PIS]	1	21 February 2017
Participant information sheet (PIS) [Phase I CYP PIS Words only]	1	21 February 2017

(13-18 years)]		
Participant information sheet (PIS) [Phase II CYP PIS words only (13-18 years)]	1	21 February 2017
Participant information sheet (PIS) [Phase I CYP PIS Leaflet (9-12 Years)]	1	21 February 2017
Participant information sheet (PIS) [Phase I CYP PIS words and symbols (4-8 Years)]	1	21 February 2017
Participant information sheet (PIS) [Phase II PIS words and symbols (4-8 years)]	1	21 February 2017
Participant information sheet (PIS) [Phase I CYP Symbols only (Communication difficulties)]	1	21 February 2017
Participant information sheet (PIS) [Phase II CYP PIS Leaflet (9-12 years)]	1	21 February 2017
Research protocol or project proposal [Research Protocol]	1	21 February 2017
Response to Request for Further Information [Clarifications to IRAS form]		29 March 2017
Summary CV for Chief Investigator (CI) [CV CI]		08 March 2017
Summary CV for supervisor (student research) [CV Eleanor Main]		
Summary CV for supervisor (student research) [CV Kate Oulton]		
Validated questionnaire [Cerebral Palsy Quality of Life Parent/Carer (4-12 years)]	1	
Validated questionnaire [Cerebral Palsy Quality of Life Child (9-12 years)]		
Validated questionnaire [Cerebral Palsy Quality of Life CYP (13-18 years)]		
Validated questionnaire [Cerebral Palsy Quality of Life Parent/Carer (13-18 years)]		
Validated questionnaire [Participation and Environment Measure - Child and Youth]		

A. Parent/Carer Information Sheet

The Toxin Study

Understanding Clinical and Patient Reported Response of Children and Young People with Cerebral Palsy to Botulinum Toxin Injections: A Longitudinal Observational Study

[We would like to invite you and your child to participate in this research study.](#)

This study is looking at the use of Botulinum Toxin Injections in children and young people with cerebral palsy who can walk (either on their own or with walking aids). Before you decide whether you would like to participate it may be helpful to understand why this research is being done and what will be asked of you and your child if you decide to participate.

Please take the time to read this information carefully and take home a copy of this. You may wish to discuss your choice with your family and friends. This patient information sheet describes the purpose, procedures, benefits, risks and safety issues of the study.

[What is the purpose of the study?](#)

Children and young people with cerebral palsy often have muscle stiffness. This can cause movement difficulties and limit the activities they can do. Botulinum Toxin A (also known as 'botox' or 'toxin') can be injected into muscles to temporarily reduce muscle tightness, pain and in some cases make movement easier. The chemical effect of botulinum toxin is temporary, lasting a few months, which means injections may need to be repeated. The time for this varies between 4 - 12 months and in some cases longer.

We know that botulinum toxin can be successful in reducing muscle stiffness in children with cerebral palsy. What we do not know, is whether reducing this muscle tightness actually makes life easier for children and young people with cerebral palsy. Does it change how much they can do (activity) or how much they can join in at home, school and in the community (participation)? We want to know how long any changes last and whether our measurements in clinic pick up the important things that matter to children and young people with cerebral palsy and their families?

There has been little research looking at how Botulinum Toxin injections can influence a child's life with cerebral palsy and even less research has looked at change over a twelve month period.

When you have read this information you will be given the opportunity to ask questions. If you decide to take part and allow your child to participate in the study, you will be asked to sign a consent form. You will be given a copy of the consent form and the original will be kept as part of your child's medical records.

Why have we been invited to take part?

We have invited you to participate in this study because your child has a diagnosis of cerebral palsy and has been assessed as having muscle stiffness which may benefit from treatment with Botulinum Toxin A injections.

We are inviting parents with children who have a diagnosis of cerebral palsy, aged between 4 and 18 years, who are able to walk (with or without walking aids) and are under the care of Motor Disorders Service at Great Ormond Street Hospital.

Do we have to take part?

No, you do not have to take part. Participation is completely voluntary which means you are free to decide whether or not you would like to take part. If you and your child say yes now, you are free to stop at any time without giving a reason. This will not affect your child's current or future care or inclusion in any future research projects.

What will we be asked to do if we agree to take part?

We will only ask your child to take part if you agree for us to invite them. We have a separate information sheet for children and young people, which will help to explain to your child their involvement in more detail.

Your child's Botulinum Toxin treatment will follow the usual routine clinical practice for children attending the motor Disorders Service at GOSH. The team will carry out the usual assessments for your child in clinic, once before injection and at 6 weeks, 6 months and 12 months post injection.

With your permission we would like to use this data collected in clinic for the study. In addition to our usual clinical practice, we will ask you and your child to complete a standardised questionnaire (see below) at the time of each clinic appointment.

These Questionnaires are;

Cerebral Palsy Quality of Life questionnaire (CPQOL)

We are very interested in how your child feels about their quality of life and not just about their stiff muscles. The Cerebral palsy Quality of life questionnaire (CPQOL) has been specially developed for use with children with cerebral palsy and we will ask your child (with your help) to complete this. This should take **~20 minutes** to complete.

Participation Environment Measure – Children and Youth (PEM-CY)

We want to know how your child joins in (participates), in a variety of settings such as home school and community. We will ask you (with your child's help) to complete a standardised Participation questionnaire (PEM-CY). This should take **~20-30 minutes** to complete.

These questionnaires can be completed in the hospital (paper form or electronically) or at home (paper only) and brought to the hospital on your next visit, whichever you and your child prefer.

Goal setting

As per our usual clinical practice, you and your child will have an opportunity to explore the main physical difficulties that your child experiences. Three goals will be set during the pre-injection appointment and will be revisited at each clinic assessment. These will target areas which you hope the botulinum toxin injections can help.

We have also added an additional assessment tool to be completed by the researcher; The Quality Function Measure (Quality FM). This tool will assess the *quality* of your child's movements in more detail. It will be scored from the video recording of your child's standardised Gross Motor Function Measure (GMFM) which takes place in clinic as part of our usual clinical practice. This will not involve any extra movement tests for your child and is scored by the researcher following the clinic appointment.

What are the possible risks and benefits of taking part?

We will gather information about the benefits of botulinum toxin injections for children with cerebral palsy. Whilst we cannot guarantee that this will help your child, we believe the information will help to guide treatment for children with cerebral palsy in the future, here at Great Ormond Street Hospital and other hospitals providing Botulinum Toxin injections. Additionally, some children and their parents who take part in this study will have the opportunity to be interviewed in phase II. They will be invited to talk about their experience of

botulinum toxin injections in more detail, which they may find helpful. Please let us know if you and your child would be interested in being considered for this phase of the study.

There are no known risks for you or your child in taking part in this research study. At the end of each assessment, you will be informed of your child's progress as per usual clinical practice. The plan for future treatment (including re-injection) will be based on clinical indication together with your preference and the input of your child's local team. Participating in this study will not change your child's clinical treatment.

Will taking part in this study be confidential?

With your permission we will inform your local team that you are taking part in this study. All information which is collected about your child during the course of the research will be kept strictly confidential, which means only the research team will be able to see it. Any data we gather will have your child's name and address removed (and replaced with codes). If we share any results, these will be kept anonymous so that you or your child cannot be identified.

How will the data be kept secure and what happens to the data at the end of the study?

All paper data will be stored in a locked filing cabinet, which is located in The Motor Disorders office at Great Ormond Street Hospital. This is only accessible by a swipe card. Personal identifiable data and consent forms will be stored separately to research data. Electronic data is stored on password protected servers accessed by Trust computers and encrypted laptops. At the end of the study personal data will only be stored and accessed for up to 12 months. Research data will be stored for 15 years or in accordance with GOSH Trust policies.

Can we withdraw from the project?

Yes, your participation is entirely voluntary. You are free to withdraw from the study any time without having to give a reason. If you choose not to enter the study, or to withdraw once entered, this will in no way affect your child's future medical care. However, with your permission we would still like to use the data collected up to that point.

What will happen to the results of the study?

All the families who take part will receive a report of the findings. The results will also be published and presented so they can be shared with other healthcare professionals and researchers as well as special interest groups such as SCOPE and Hemi help. The National

Institute of Health Research (NIHR), who has funded this study, will receive a full study report. All data that is shared will be anonymised so that children and families cannot be identified.

Who has funded and reviewed this research project?

This research has been funded by a National Institute of Health Research (NIHR) Clinical Doctoral Research Fellowship and has been reviewed by independent researchers as part of the process of applying for funding. The study is supported by the Movement Disorders Service, Wolfson Neurodisability Service at Great Ormond Street Hospital.

Lesley Katchburian(chief investigator), is carrying out this project as part of a research doctorate programme supervised by Professor Eleanor Main (details below).

Ethical approval has been gained for this study from . [REDACTED]

What if I have any questions about the study?

If you have any additional questions please contact Lesley Katchburian

What if I have any concerns about the study?

If you have any concerns or other questions about this study or the way it has been carried out, please talk to a member of the research team or your clinical team. If you remain unhappy, or wish to comment in any other way, you can contact the Patient Advice and Liaison Service (PALs) on 020 7829 7862 or email: pals@gosh.nhs.uk

Contact for further information: [REDACTED]

Thank you for reading this and considering whether to let your child take part in the project.

B. Children and Young Person's Information Sheet

The Toxin Study



Understanding clinical and patient reported response of children and young people with cerebral palsy to Botulinum Toxin injections: a longitudinal observational study

[We would like to invite you to take part in a research study.](#)

This study is looking at the use of Botulinum Toxin Injections in children and young people who have cerebral palsy. Before you decide whether you would like to join in with this study, it may help to understand why the research is being done and what it would involve for you.

Please read the following information leaflet carefully – it tells you what will happen if you decide to take part. Take time to consider whether or not you would like to be involved and talk to others about taking part if you wish. Please ask us if there is anything that is not clear or if you would like more information.

[What is the purpose of the study?](#)

Some children and young people with cerebral palsy have difficulty moving and taking part in activities because of muscle tightness or stiffness. Botulinum Toxin A (a medicine also known as 'botox' or 'toxin') is injected into muscles to reduce muscle tightness, and make movement easier. The effects of toxin injections are temporary, lasting a few months, which means sometimes the injections need to be repeated.

What we would like to know in this study is....

Does reducing the tightness in your muscles make life easier for you?

Do injections change how much you can do or how much you can join in at home, at school or out in the community with your friends and family?

How long do any changes last after the injections?

We would also like to know if what we measure in the hospital clinic picks up the important things that matter to you and your family following your injections.

When you have read this information you will be given the opportunity to ask any questions you may have. You will then be asked to sign an assent form if you decide to take part in the study. You will be given a copy to keep and the original will be kept as part of your medical records.

Why have I been invited to take part?

We are inviting children and young people (aged between 4 and 18 years) who have cerebral palsy and are due to have Botulinum Toxin A injections at Great Ormond Street Hospital.

Do I have to take part?

No, you do not have to take part. Participation is completely voluntary which means you are free to decide whether or not you would like to take part. If you say yes now, you are free to stop at any time without giving a reason.

What will I be asked to do if we agree to take part?

We will do all the usual tests in clinic, once before you have your injection and the same ones again at 6 weeks, 6 months and 12 months after your injections. This is the same as our usual clinical practice for children receiving botulinum toxin injections. We want to see if the Botulinum toxin injections have changed anything about the way you move and we want to see how long these changes last.

As part of this study we have added two questionnaires to be filled in around the time of each clinic appointment. There will be one questionnaire for you to fill in about how happy you are feeling about your movements and another one for your parents to fill in about how much you are doing at home at school and around your neighbourhood. You can help them to answer the questions if you would like to.

There is no need to worry about filling in your questionnaire because you can always ask someone to help if you need it. You can answer your questionnaire at home or in the clinic it's up to you.

We have also added a new assessment score about the quality of your movements after injections. Do not worry, this will not mean you have to stay any longer than usual in the clinic! The researcher can do this later by looking at the video recording taken in clinic of your movement tests.

At your 6 month appointment you may be asked to take part in an additional part of the study which will involve a short interview. We will ask about any changes you might experience following botulinum toxin injections, to see if they match up with what the tests in clinic tell

us. Please let us know if you are interested in being asked to join the second part of the study.

How long will I be asked to take part for?

We would like to see you for once before your injections and then 3 times afterwards just to check how you are getting on.

What are the disadvantages of taking part?

Taking part in our study means you will have to give up some time to fill in a questionnaire every time you have a clinic appointment. We think it will take you about 15-20 minutes. You can do this at home or when you are at the hospital waiting for your appointment - whichever suits you best.

What are the advantages of taking part?

By taking part in the study you will help us gather information about the changes that happen following botulinum toxin injections. We believe that the information you give us will help to guide treatment for children with cerebral palsy in the future, here at Great Ormond Street Hospital and other hospitals who give Botulinum Toxin injections.

Additionally, some children and their parents who take part in this study will also have the chance to be interviewed. They will be able to talk about their experience of botulinum toxin injections in more detail, which they may find helpful.

Will taking part in this study be confidential?

Yes. All information collected about you during the study will be kept confidential, which means only the research team, will be able to see it. Any data we collect will have your name and address removed (and replaced with codes). If we share any results, these will be kept anonymous so that you cannot be identified and nobody will be able to guess it is you.

How will you keep my data secure and what happens to my data at the end of the study?

All paper data will be stored in a locked filing cabinet; this is in The Motor Disorders office at Great Ormond Street Hospital. You can only enter this office by using a swipe card. Any information which has your name on will be stored separately to research data. Electronic data is stored on computers and laptops and can only be used with passwords. At the end of the study your personal data will only be stored and accessed for up to 12 months. Research data will be stored for 15 years in agreement with the rules at Great Ormond Street Hospital.

What if I don't want to carry on with the study?

If you agree to take part in the study you can stop at any time without telling us why. If you do decide to stop, your care at the hospital will not be affected in any way. However, if you and your family agree we would still like to use the data collected up to that point.

What will happen to the results of the study?

You will receive a report of the findings. The results will also be shared with other healthcare professionals and researchers.

Who is organising and funding this study?

This study is being carried out by Lesley Katchburian (Clinical Specialist Physiotherapist) and The Motor Disorders Team at Great Ormond Street Hospital. The research has been funded by a National Institute of Health Research (NIHR) Clinical Doctoral Research Fellowship.

Lesley Katchburian, chief investigator is carrying out this project as part of a research doctorate programme supervised by Professor Eleanor Main (please see her details below).

Ethical approval has been gained for this study from [REDACTED]

Who should I contact with any questions?

You can contact Lesley either by



[REDACTED]

or 

[REDACTED]

Contact for further information:

[REDACTED]

Thank you for taking the time to read this information leaflet!

What should I do know?

Now that you have read about the study, you can think about whether or not you want to take part. Maybe talk about it with other people before you decide.

If you think you DO want to take part, let us know and we can arrange to meet you. If not, that is fine.

Thank you for taking the time to read this leaflet.

If you are thinking about taking part and would like more information or you have any questions about the study please contact **Lesley Katchburian** (Chief Investigator) on



Or write to Lesley at

The Motor Disorders Service, The Wolfson Neurodisability Service, Level 10 Nurses Home, Great Ormond Street Hospital, Great Ormond Street WC1N 3JH

Funded by the National Institute of Health Research
The study has been reviewed and approved by ...

The Toxin Study

Understanding the use of botulinum toxin injections in children and young people with cerebral palsy

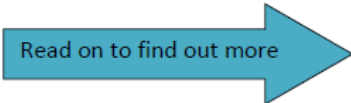


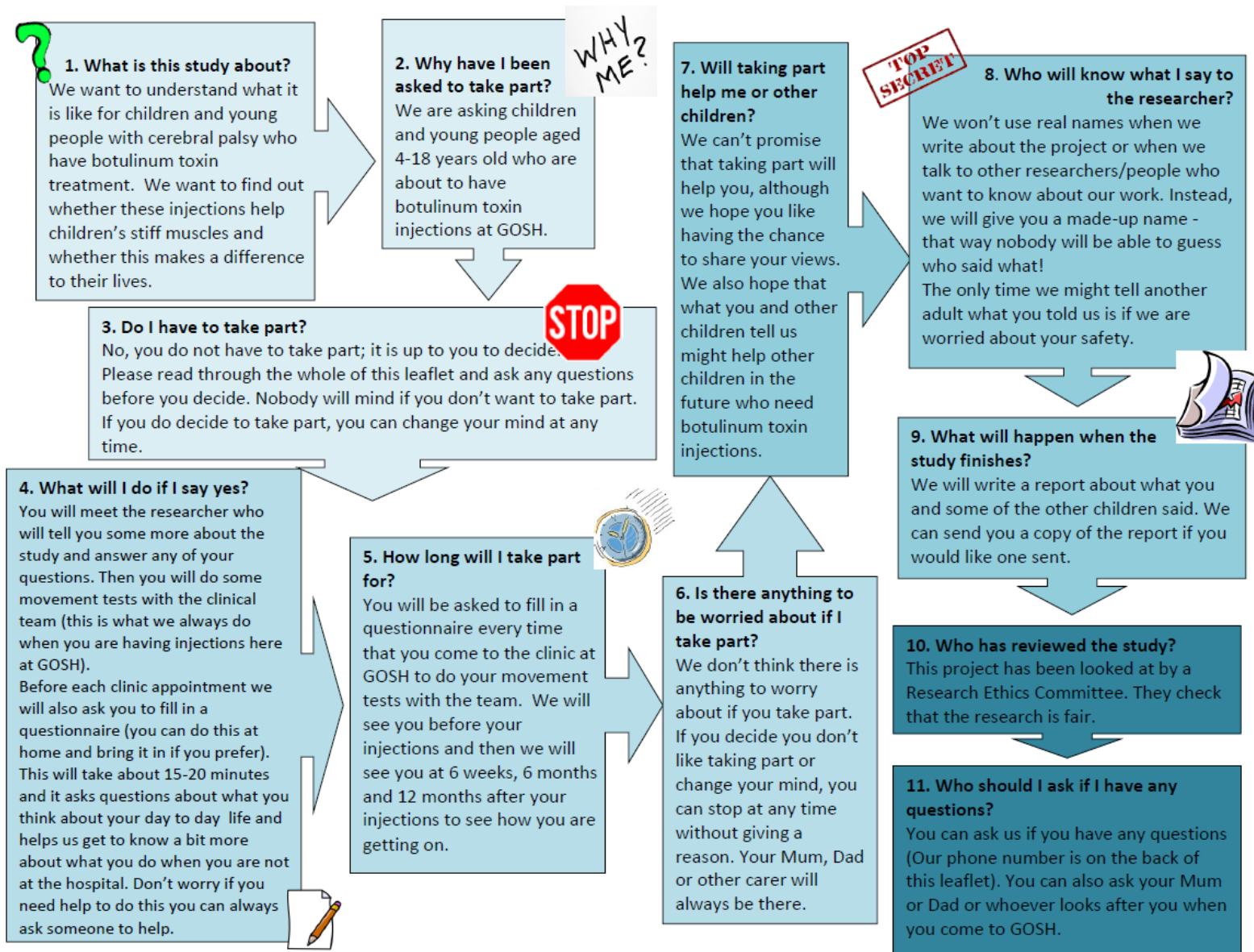
Hello my name is Lesley

I am a physiotherapist and I work in the Motor Disorders Service here at Great Ormond Street Hospital. I would like to invite you to take part in a research project. Before you decide if you would like to take part or not, it is important that you know why we are doing this project, and what taking part would involve.

This leaflet tells you more about what would happen if you decide to take part. You can talk to other people, like your mum or dad or one of the physiotherapists or doctors, about taking part and you can ask us any questions you may have.



Read on to find out more 



CYP PIS Words and symbols 4-8 years

Version 1 Phase 1 21.2.017

The Toxin Study

Understanding the use of botulinum toxin injections in children and young people with stiff muscles

Hello, my name is Lesley



I am doing a research project with a group of children and young people at Great Ormond Street Hospital.



Research helps us to find out answers to important questions.



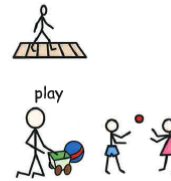
I would like you to help me with my research.



You can say Yes or No. Your Mum or Dad can help you decide.

What do you want to know?

I want to know if botulinum toxin helps your leg muscles and makes it easier to move or join in with your friends and family.



I want to know how long any changes last after your botulinum toxin treatment.



What would I have to do?

If you take part, you will do all the movement tests in clinic that we usually do when you come for botulinum toxin treatment.



If it is OK I will ask you to fill in a form (a questionnaire). This helps us to know more about what you do when you are at home.



Will you tell anyone what I say?

I won't tell anyone what you say, but if you tell me that someone has hurt you, I might have to tell someone else.



What do I do now?

If you do not want to take part that is OK. You do not need to do anything. No one will be upset or cross with you.



If you want to take part or have any questions ask us or ask your Mum or Dad to talk to the team. They can ask me to come and talk to you, next time you are in the hospital.



Remember, if you agree to take part it is OK to stop at anytime




Thank-you very much for reading this leaflet



Examples of Consent/ Assent forms

C. Parent Consent Forms



Great Ormond Street 
Hospital for Children
NHS Foundation Trust

CONSENT FORM for PARENTS/CARERS

Understanding clinical and patient reported response of children and young people with cerebral palsy to Botulinum Toxin injections: a longitudinal observational study

		YES	NO
1.	I confirm that I have read and understood the information sheet (v1 1.2.2017) for the study titled above and have had the opportunity to ask questions and have had these answered satisfactorily.		
2.	I confirm that I have had sufficient time to consider whether I will take part in the study.		
3.	I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected.		
4.	I agree to complete a questionnaire regarding my child's level of participation at each clinic appointment.		
5.	I agree to assist my child complete a quality of life questionnaire at each clinic appointment.		
6.	I understand that any direct quotes from me in goal setting or questionnaires will be completely anonymous and kept confidential, and I agree for these to be used for educational purposes connected to this study e.g. presentations, training, publications if names are removed.		
7.	I confirm that if I decide to stop taking part in the study that any questionnaires I have completed will be included in the data unless I ask for them to be withdrawn.		
8.	I agree to you contacting my child's GP to let them know my child is participating in the study.		
9.	I agree to you contacting my child's Physiotherapist to let them know my child is participating in the study and to ask for their feedback regarding my child's therapy.		
10.	I agree to be contacted regarding participation in phase II of the study 6 months after my child's injections.		
11.	I agree to take part in the above study.		

Full name of Child _____

Full name of Parent/Guardian Date Signature

Date Signature Researcher

Patient Assent Form

Version 1 21.2.2017 Phase 1

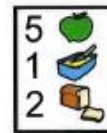
The Toxin Study

Understanding the use of botulinum toxin injections in children and young people who have stiff muscles

I have read the information sheet



I understand what Lesley is asking me to do




I am happy to take part



I know that I can stop at anytime




Child/Young person


Parent/Carer
parent/carer








.....Lesley (Researcher)

Date:




/

Children and Young People's Assent Form

Understanding clinical and patient reported response of children and young people with cerebral palsy to Botulinum Toxin injections: a longitudinal observational study

		YES	NO
1. I have read the information sheet for this study and have had the chance to ask questions and someone has answered these for me.			
2. I have had enough time to think about whether or not I wish to take part.			
3. I know what I will be asked to do if I say Yes.			
4. I know that I do not have to say Yes. If I do say Yes I know I can stop at any time and no one will be upset or angry with me.			
5. I know that what I share with you will be kept confidential which means only the research team will be able to see it. But, if I say anything that makes you worried about my safety you may have to tell someone else.			
6. I agree to fill in a form and answer some questions and about how I feel about my movements. I know I can ask someone to help me if I need it.			

One copy to be kept by participant; one copy to be kept by researcher; one copy in the medical notes

7. I agree for you to share some of the things I have said with other researchers, students and professionals so they can learn but only if you do not use my real name.			
8. I agree for you to video the movement activities I do in clinic.			
9. I agree to take part in the above study.			

If any answers are NO or you don't want to take part, don't sign your name!
If you DO want to take part you can write your name below

Full name of Young Person

Full name of Parent/Carer

Date

Signature

Full name of Researcher

Date

Signature

Thank you for your Help



One copy to be kept by participant; one copy to be kept by researcher; one copy in the medical notes

14.3 Study Manual

Example of recruitment protocol- instructions for clinicians

RECRUITMENT THE TOXIN STUDY



Is the child on the waiting list for lower limb Botulinum Toxin Injections? Do they have an injection date planned? Do they meet the eligibility criteria below?

If **YES** ...please ask Admin to send family an invitation letter (A) to join the study and a Patient Information Sheet (B) together with their pre-injection appointment letter.

Or if letter already sent Clinical staff to phone family and ask if they are happy to talk to researcher about the study.

Eligibility Criteria

Inclusion Criteria

CYP

- Confirmed diagnosis of CEREBRAL PALSY (Unilateral or bilateral CP) with hypertonia (due to spasticity +/- or dystonia)
- GMFCS level I,II or III
- 4-18 years
- Requiring lower limb BoNT-A injections for dynamic hypertonia interfering with lower limb functional goals or causing pain (**patients can also be receiving U/L injections at the same time**)

Exclusion Criteria

CYP

- History of previous orthopaedic surgery to the injected muscle in last 12 months
- History of previous neurosurgery for tone reduction in last 12 months
- Lower limb BoNT-A injections in previous 12 weeks
- Unrelated musculoskeletal problems, such as recent acute injury, or congenital structural deformity
- Contra indications to BoNT-A treatment
- Fixed muscle Contracture with no dynamic component
- Unable to complete baseline assessments

Parents/carers

Insufficient knowledge of English language to complete outcome measure

The family can confirm they are happy to discuss the study with LK (or research team member in her absence) either by filling in the form attached to Invitation letter A or letting NDS Admin team know when they phone to confirm the appointment.

Notes for Research Team member

....Please explain that

.....our service has been established for 20 years and although we understand that Botulinum Toxin can have a positive effect in relaxing stiff muscles, what we really want to know is whether this change in the muscle affects other areas of a child's life? For example how much they can move about, whether it helps them to join in with their friends and family and how long the effects of the botulinum toxin injections last in different children.

We hope that this study will give us more information about Botulinum Toxin treatment and help us improve the service for children and their families.

1. Explain to the family that this study attempts to mirror usual clinical practice. We will carry out all the usual standardised assessments and we will do this at their child's
 - a. Pre-injection appointment
 - b. 6 weeks post injection
 - c. 6 months post injection
 - d. 12 months post injection
2. Parents should be reassured that at each stage their child's participation in the study will not affect their access to Botulinum Toxin -A treatment, treatment will continue to be provided as clinically indicated.
3. Check families have been provided with an invitation letter (A), Parent information sheet (PIS) (B) and an age appropriate child information leaflet (C).
4. Explain to the family who are considering taking part in the study that they will be asked to complete the additional questionnaires introduced for the study at the 4 assessments as well as provide COPM goal scores. This will be gone into in more detail at the pre-injection appointment when consent is taken.

THANKYOU



A. Instructions for each assessment time point T0-T3

Pre-injection Assessment for Toxin Study Patients

T0 CHECKLIST

START ICP

Any change since last Assessment

Mobility & Activity levels (FMS)

Function (MACS, GMFCS)

Pain (FPS-r)

Medication

Therapy

MOVEMENT TESTS REQUIRED IN CLINIC

- 1 MINUTE FAST WALK TEST (1MFWT)
 - Measure distance walked
- VIDEO GAIT
 - Frontal & Saggital Plane (with and without orthotics)
- TIMED UP AND GO (TUG)
 - Timed only does not require a video
- GMFM (D&E DIMENSIONS ONLY FOR QFM**)
 - Please Film 2 trials where possible (look at video angles in manual)

**primary outcome measure

PASSIVE EXAMINATION

- Range of motion measured using a goniometer
- Must measure Modified Tardieu (MTS) & Ashworth (MAS) for muscles to be injected
- Look at muscle selectivity and score with Selective Motor Scale (SMC)

CLINICAL DECISION MAKING POST ASSESSMENT

- Muscle Selection
- Goal setting using COPM**
 - Family to select 3 Goals hoping to change post injection and give Performance & Satisfaction Score
- Consider Additional Interventions required to potentiate toxin

** primary outcome measure

Families will be given participation (PEM-CY) & Quality of life (CPQOL) Questionnaires to take home and complete prior to/on injection day

First Post-injection Assessment for Toxin Study Patients

T1 CHECKLIST

ICP

- Review Day case procedure
- Note any side effects
- Record **ANY** change since last Assessment (+/-)
- Mobility, function & Activity levels
- Pain (FPS-r)
- Medication
- Therapy provision
Frequency/type/location

MOVEMENT TESTS REQUIRED IN CLINIC

- 1 MINUTE FAST WALK TEST (1MFWT)
 - Measure distance walked
- VIDEO GAIT
 - Frontal & Saggital Plane (with and without orthotics)
- TIMED UP AND GO (TUG)
 - Timed only does not require a video
- GMFM (D&E DIMENSIONS ONLY FOR QFM**)
 - Please Film 2 trials where possible (look at video angles in manual)

**primary outcome measure

PASSIVE EXAMINATION

- Range of motion measured using a goniometer
- Must measure Modified Tardieu (MTS) & Ashworth (MAS) for muscles to be injected
- Look at muscle selectivity and score with Selective Motor Scale (SMC)

CLINICAL DECISION MAKING POST ASSESSMENT

- Reflect on muscle selection – has toxin reached threshold effect?
- Revisit Goal setting using COPM**
 - Family to score 3 Goals selected at pre injection assessment and give Performance & Satisfaction Score – family can add additional goals if already achieved set goals
- Consider Additional Interventions required to potentiate toxin

Families should have been given participation (PEM-CY) & Quality of life (CPQOL) Questionnaires to take home and complete following injection day. Please provide another if not completed /ask Researcher to send via email.

Second and Third Post-injection Assessment for Toxin Study Patients

T2/T3 CHECKLIST

ICP

- Record ANY change since last Assessment (+/-)
- Mobility, function & Activity levels
- Pain (FPS-r)
- Medication
- Therapy provision
Frequency/type/location
- Orthotics/ casting/FES

MOVEMENT TESTS REQUIRED IN CLINIC

- 1 MINUTE FAST WALK TEST (1MFWT)
 - Measure distance walked
- VIDEO GAIT
 - Frontal & Sagittal Plane
(with and without orthotics)
- TIMED UP AND GO (TUG)
 - Timed only does not require a video
- GMFM (D&E DIMENSIONS ONLY FOR QFM**)
 - Please Film 2 trials where possible
(look at video angles in manual)

**primary outcome measure

PASSIVE EXAMINATION

- Range of motion measured using a goniometer
- Must measure Modified Tardieu (MTS) & Ashworth (MAS) for muscles to be injected
- Look at muscle selectivity and score with Selective Motor Scale (SMC)

CLINICAL DECISION MAKING POST ASSESSMENT

- Family to score COPM** Goals selected at pre injection assessment and give Performance & Satisfaction Score
- Reflect on muscle selection /response to toxin- retention of benefits?
- Consider Follow up required
 - Still showing a response – review at later date *
 - Further injections required – consider timing within next 6 months
 - Referral onto other services (e.g. orthopaedics, MDC)
 - Discharge back to local team

Families should have been given participation (PEM-CY) & Quality of life (CPQOL) Questionnaires to take home and complete following post injection review. Please provide another if not completed /ask Researcher to send via email

**All non surgical study patients will be reviewed at 12 months post injection

B Study Assessments- Instructions for Clinicians



1 minute fast walk test

MEASURES THE EFFICIENCY OF GAIT: The One Minute Fast Walk Test (1MFWT) is considered a good discriminator of functional ability for dynamic balance, muscle performance and endurance

The test involves a five minute rest, followed by walking for one minute at maximum walking speed without running. Children are able use normal walking aids and wear orthoses. Distance is calculated to the nearest metre. We are going to use the corridor outside level 4 gym traffic permitting!

Instructions:

“Walk at your fastest pace without running”



Modified Timed up and go (mTUG) Also known as TUG in children (TUG-IC)



Purpose: To test functional ambulatory mobility including balance and difficulty turning during gait of children with or without physical disabilities and to monitor change over time. It requires both static and dynamic balance.

The test consists of a pre-test to familiarize the patient with the procedure.

Children can use their usual walking aids shoes & orthoses. The chair used is a height that supports hip and knee flexion of 90 degrees *

The child is not instructed on how fast to walk and the test may be restarted if the child skips or hops instead of walks during the test.

The child is instructed to

“stand up, walk forward and touch the star on the wall then walk back to the chair and sit down”.



The star should be at child’s shoulder height and is 3 metres from the chair/bench.

The timer is started when the child begins the movement to stand (not necessarily when the child’s bottom leaves the chair) after the cue “ready, steady, go” and is stopped when the child’s bottom touches the chair again.

We can give them up to 3 trials and record the best in the ICP.

Selective Motor Control Test (SMC)

Test Procedure

The Boyd and Graham Selective Motor Control test – test protocol (movement: dorsiflexion)

Description

The child sits with hips flexed and knees comfortably extended, able to see their feet. The child is requested to dorsiflex each foot individually to a target. The limb is in vision and the balance of muscle activity is observed.

SCORING SMC

0	No movement when asked to dorsiflex the foot
1	Limited dorsiflexion using mainly extensor hallucis longus and/or extensor digitorum longus
2	Dorsiflexion using extensor hallucis longus, extensor digitorum longus and some tibialis anterior activity
3	Dorsiflexion achieved using <i>mainly tibialis anterior activity</i> but accompanied by hip and/or knee flexion
4	Isolated selective dorsiflexion achieved, through available range, using a balance of tibialis anterior activity <i>without</i> hip and knee flexion



Tips

Make sure that the child is comfortable. They can be sat on the plinth with the back rest to support them and if required a small support under their knee. Encourage the child to pull up their foot and touch a toy.

Modified Ashworth Scale MAS

NORMAL	0	No increase in Muscle tone
MILD	1	Slight increase in muscle tone- manifesting as a 'catch and release' or by minimal resistance at the end of range of movement when the part is moved.
	1+	Slight increase in muscle tone- manifesting as a 'catch' followed by minimal resistance throughout the remainder (less than half) of range of movement.
MODERATE	2	More marked increase in muscle tone through most of the range of movement but part easily moved.
SEVERE	3	Considerable increase in muscle tone passive movement is difficult
	4	Rigid part cannot be moved



Tips

1. Always try to take first measurement for each muscle group being tested (max 3 trials)
 - a. If we continue to assess in an attempt to get an average the muscle tone will reduce
 - b. Speed should be the same as limb falling with gravity 'fast'
2. Tone is variable so we know it will change depending on day etc. but we should standardise position tone measured – make a note on ICP if position differs from usual.
3. Contractures vs increased Tone
 - a. Record the MAS score within the available range.
 - b. Start in maximal position for muscle i.e. if measuring plantiflexors start in full plantarflexion; adductors – full adduction etc.

C. GOSH Protocol of standardised musculoskeletal examination for Hamstring and Gastrocnemius

muscles- Showing Fast and Slow stretch for Modified Tardieu Scale (R1 and R2) (photos

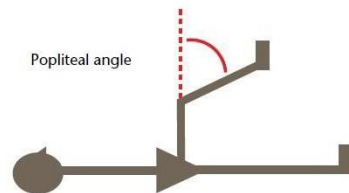
Popliteal Angle

Starting position: supine with leg to be measured flexed to 90° and contralateral limb lying passively on the plinth. Extend the limb to be measured to its maximum, the angle measured is between the shank and the vertical, if the leg extends so that the knee is straight the angle is 0°.

The fulcrum of the goniometer is placed over the lateral aspect of the knee joint with the fixed arm aligned with the femur towards the greater trochanter and the moving arm is placed along the fibula aligned with the lateral malleolus.

R1 should be measured.

Hamstring length



Popliteal angle



Fast popliteal angle (R1)

Ankle Dorsiflexion

With knee flexed

Starting position: Hip and knee flexed to 90°, stabilise the subtalar joint by holding the calcaneus in neutral, supinate the forefoot to prevent movement of the intertarsal joints and dorsiflex the foot towards the vertical.

With knee extended

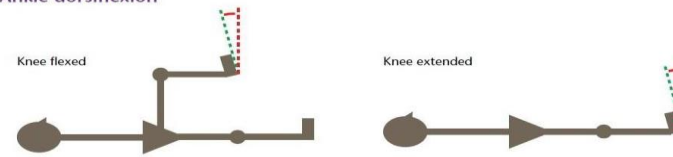
Starting position: Hip and knee extended, stabilise the subtalar joint by holding the calcaneus in neutral, supinate the forefoot to prevent movement of the intertarsal joints and dorsiflex the foot towards the vertical.

The fulcrum of the goniometer should be placed inferior to the lateral malleolus towards the sole of the foot with the fixed arm aligned with the lateral malleolus and the fibula, the moving arm over the lateral border of the foot up to the base of the 5th metatarsal to prevent a mid-foot break producing an erroneous measure.

Beware the subtalar joint slipping in to valgus to allow an increased measure of dorsiflexion.

- A 90° angle is recorded as 0° of dorsiflexion.
- If dorsiflexion is lacking e.g. -5° or note 5° PF.
- R1 should be measured with knee extended.

Ankle dorsiflexion



Ankle dorsiflexion – knee flexed



Ankle dorsiflexion – knee extended



Fast – plantarflexors (R1)



14.4 QFM Scoring

A. Example of QFM structure and scoring

Generic scoring for each attribute

0 = a lot of difficulty (markedly atypical)

1 = some difficulty (moderate atypical)

2 = a little difficulty (slightly atypical)

3 = no difficulty (looks fine)

Example of item specific scoring

GMFM 69 Walks forward 10 steps

LE Alignment:

Focus on alignment in weight bearing leg:
hips, knees, ankle, pelvis at peak mid stance.
Score alignment based on most involved leg.

1st trial 2nd trial Average

--	--	--

Co-ordination:

Look carefully step rhythm, accurate foot placement.
arm swing and arm sequencing with legs, and overall
ease of movement. Is the gait pattern smooth?

**Very slow gait needs to be marked down to a '1'
even if well-targeted, i.e., more than 2 seconds
between steps.**

1st trial 2nd trial Average

--	--	--

Dissociated movement:

Should see heel-toe pattern with each step,
and flexion/extension action at hip and knee
through stance and swing phases (segmental
movement). Watch for compensatory trunk or
pelvic rotation.

1st trial 2nd trial Average

--	--	--

Stability:

Line of progression gives cues about stability.
Should be a straight line of steps! No veering off.
Are the arms used for balance for any/all of the task?

**If needs to be supported (by table, wall, person)
at end of 10 steps, score '1'.**

**If they complete at least 3 steps before being
assisted, score '1'**

Side steps/protective steps may indicate an issue

1st trial 2nd trial Average

--	--	--

Weight shift:

Two directions of movement: forward/backward
and lateral onto the weight bearing leg.

Watch for: backward lean, inappropriate
lateral weight shift such as Trendelenberg.

Uneven stance time may reflect issues with weight
shift. Subtle weight shift issues during gait may
present as vaulting in which vertical excursion is
increased, or there may be lack of heel-toe pattern
(i.e. insufficient weight transfer forward through foot).

1st trial 2nd trial Average

--	--	--

B. QUALITY FM™ SUMMARY SCORE CALCULATION

Item	Alignment (A) 14 items	Co-ordination (C) 31 items	Dissociated Movement (D) 16 items	Stability (S) 30 items	Weight Shift (W) 25 items
SUM OF RAW SCORES	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
NUMBER OF 'NOT TESTED' ITEMS*	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
NOT TESTED SCORES X 2	A = <input style="width: 80%;" type="text"/>	C = <input style="width: 80%;" type="text"/>	D = <input style="width: 80%;" type="text"/>	S = <input style="width: 80%;" type="text"/>	W = <input style="width: 80%;" type="text"/>
DIVIDE SUM OF RAW SCORES	$\frac{\text{Sum}}{42-A}$ <input style="width: 80%;" type="text"/>	$\frac{\text{Sum}}{93-C}$ <input style="width: 80%;" type="text"/>	$\frac{\text{Sum}}{48-D}$ <input style="width: 80%;" type="text"/>	$\frac{\text{Sum}}{90-S}$ <input style="width: 80%;" type="text"/>	$\frac{\text{Sum}}{75-W}$ <input style="width: 80%;" type="text"/>
	<input style="width: 80%;" type="text"/> x100	<input style="width: 80%;" type="text"/> x100	<input style="width: 80%;" type="text"/> x100	<input style="width: 80%;" type="text"/> x 100	<input style="width: 80%;" type="text"/> x 100
PERCENT ATTRIBUTE SCORE	<input style="width: 80%;" type="text"/> % ALIGNMENT	<input style="width: 80%;" type="text"/> % CO-ORDINATION	<input style="width: 80%;" type="text"/> % DISSOCIATED	<input style="width: 80%;" type="text"/> % STABILITY	<input style="width: 80%;" type="text"/> % WEIGHTSHIFT

AN OVERALL TOTAL SCORE IS NOT CALCULATED

**Note: All Stand and Walk items should either be tested or assigned a GMFM and Quality FM score of 0 if the item is too difficult for the child to attempt. The 'not tested' option on the GMFM/Quality FM should be reserved just for items that were not tested due to time or fatigue issues.*

C. Site specific modified QFM filming schedule

Site specific modified QFM filming schedule – page 1		
<p>NB: ensure video clip captures both the preparation and end phase of performance for each item</p> <p>Hands on equipment or mobility aid <u>can</u> be used if required for items highlighted with *</p> <p>[modification of GMFM instructions]</p>		
ITEM	VIDEO ANGLE	SPECIAL INSTRUCTIONS
52. Pulls to stand at large bench	Back Side	Ask child to try to hold a steady stand position to finish.
54. Standing holding bench, lifts right foot	Back Left side	Make sure child not holding on with two hands when leg is first lifted.
55. Standing holding bench, lifts left foot	Back Right side	Video from side of weight bearing leg: Subject may need to move to parallel bars or to short end of plinth or to stand side on to plinth to allow lateral view
65. Cruises 5 steps to right	Back Side	Use parallel bars where appropriate to allow lateral views
66. Cruises 5 steps to left	Back Side	Use parallel bars where appropriate to allow lateral views
59. Sitting on small bench, attains standing without use of arms	Front/Back Side	Ask child to try to hold a steady stand position to finish. Film from back for GMFCS III cases requiring bench use. Position small bench near high plinth or parallel bars for GMFCSIII cases who may need to hold on for balance after assuming standing.
56. Standing: maintains, arms free, 20 seconds	Front Side	Ask child to stand quietly with arms at side for 20 seconds. Encourage child not to shift weight or move upper body <u>at all</u> once in a comfortable and stable position ("frozen statue").
53. Standing: maintains, arms free, 3 seconds	Front Side	Ask child to stand as quietly as possible with arms at side Consider omitting item for children able to stand full 20s.
57. Standing: lifts left foot, arms free, 10 sec	Front Right side	Ask child to stand as quietly as possible
58. Standing: lifts right foot, arms free, 10 sec	Front Left side	Ask child to stand as quietly as possible
62. Standing: lowers to floor with control, arms free*	Front Side	Ask child to hold steady high kneel position to start and to also hold the standing position steady with feet together at the end. Sequences for items 60-62 may be interspersed (i.e. film returning to floor between trials for coming up to standing). Subject may need to adjust position on floor to allow appropriate film angles.
60. High kneeling: attains standing through half kneeling on right knee without using arms	Front Left side	
61. High kneeling: attains standing through half kneeling on left knee without using arms	Front Right side	
63. Standing: attains squat, arms free*	Front Side	Ask child to try to come back up to a steady stand position
64. Standing: picks up object from floor, arms free, returns to stand*	Front Side	Ask child to hold steady stand position to finish Film from side of reaching arm
67. Standing: 2 hands held, walks forward 10 steps	Front Side	Tested for GMFCS III only - omit item if child able to walk hands free
68. Standing: one hand held, walks forward	Front Side	Tested for GMFCS III only - omit item if child able to walk hands free

Site specific modified QFM filming schedule – page 2		
69. Standing: walks forward 10 steps	Front Side or back	
70. Standing: walks forward 10 steps, stops, turns 180 degrees, returns	Front Side	
71. Standing: walks backward 10 steps	Front Side	
72. Standing: walks forward 10 steps carrying a large box with 2 hands	Front Side	
73. Standing: walks forward 10 consecutive steps between parallel lines 8" apart*	Front Side	Can be tested with walker
74. Standing: walks forward 10 consecutive steps on a straight line	Front Side	
75. Steps over a stick, right foot leading	Front Side (right)	Establish stick height before filming
76. Standing: steps over a stick, left foot leading	Front Side (left)	From stable standing start position near stick, child lifts leg to step over stick. Ask child to hold standing position to start, and also to hold standing position steady at end.
78. Standing: kicks ball with right foot	Front Right side	Can be tested with walker Ask child to hold steady stand position to start
79. Standing: kicks ball with left foot	Front Left side	
80. Standing: jumps 12" high, both feet simultaneously	Front Side	child to hold landing position after jump.
81. Standing: jumps forward 12", both feet simultaneously	Front Side	child to hold landing position after jump.
82. Standing: on right foot: hops on right foot 10 times within a 24" circle	Front Front	Ask child to hold steady 2-foot stand position at finish
83. Standing: on left foot: hops on left foot 10 times within a 24" circle	Front Front	Ask child to hold steady 2-foot stand position at finish
84. Standing holding 1 rail: walks up 4 steps, holding one rail, alternate feet.	Back Back	
85. Standing holding 1 rail: walks down 4 steps, holding one rail, alternate feet	Front Front	
86. Standing: walks up 4 steps, alternating feet	Back Back	
87. Standing: walks down 4 steps alternating feet	Front Front	
88. Standing on 6" step: jumps off, both feet simultaneously	Front Front	child to hold steady finish position. Should try to do this without putting hands forward onto floor.
77: Standing: runs 15 feet, stops, returns	Front/back Side at turn	Film front/back sequence in corridor

14.5 Interview Schedules

A. The Toxin Study: Interview Schedule for children and young people



NB Interviews will be more in-depth but follow usual clinical questioning and will provide children and young people the opportunity to tell their story and share their views and experiences of their life following botulinum toxin injections. The following prompts will act as guide for the researcher of issues to cover rather than a list of questions to be asked in sequential order. The language used will be appropriate to the child's age and cognitive ability. There will also be the option for children to express themselves through arts and craft activities including the use of talking mats.

Today, we are talking about your treatment with botulinum toxin

- Prompts to answer research question

Are changes dependent on age at time of injection walking ability treatment episode?

1. Is this your first injection... If no..... how many have you had before?
 - a. Are they different? Which one was the best? In what way? Why do you think that is?

- Prompts to answer research question

Does stiffness due to dystonia or spasticity change with Botulinum Toxin A injections?

Have you noticed any change in your muscles following injections? Tell me how your muscles feel...

1. Are your muscles any looser/stiffer/no change?
 - a. Has anyone else noticed? Teachers? Family? Your siblings?
 - b.
2. Do you ever get pain in the muscles in your legs?
When did you get pain in your legs? Has this changed after the injections?
3. Do you feel like you have more energy? Is it the same after the injections? Are you feeling more tired ... can you explain how?

- Prompts to answer research question
Does this make a difference to how children can function (activity) and join in (participate) with everyday life? Does this influence their quality of life?

How easily do you move around? How would you describe how much you can walk to another person?

Can you walk in the park and in the playground ? Or do you mostly walk around the classroom and at school? Or do you walk mostly with your physio community / household/ mostly therapy only?

1. How would you describe your movement activities following this set of injections Are things easier /harder/ no change?
Are there things you can do now that you found difficult before?
 - a. For example how's your walking now...change in distance/ease/quality?
 - b. Climbing stairs...support required/speed/style

...Are there other things that have been made harder for you? If yes ..what are these?

2. Has there been a change in your joining in (participation) since this last set of injections?
 - a. Thinking about activities that you usually do in school? Any changes... for example sit for longer in story time on the mat, getting ready for PE etc.
 - b. Out of school e.g. clubs? Any changes....
 - c. Anything else?

How do you think the injections have altered any activities /participation? If at all?

3. How happy are you with the activities you are able to join in with at school?
 - a. Does school help by changing the way they do things? How? Has this changed since your treatment?
 - b. Have teachers / friends/ other grown ups or anyone else in the school noticed any change?
4. How happy are you with what you do outside school? What kind of things do you do after school e.g. swimming brownies cubs etc
 - a. Has this changed since botulinum toxin?
 - b. Are there any new chances to join in with your friends or your brothers and sisters or cousins?
 - c. If yes...How has this changed following toxin injections?
5. Quality of life? How happy are you about how you can get around?

- a. Has this changed post injectionif yes when? Still now?
- b. Is it the same..worse..or better ? Why do you say that? What are the signs?

Are you still observing the same changes? If not when did it change?

Prompts to answer research question -Do we measure in clinic what is important for families?

1. When you come to clinic we do lots of movement tests to see how your movements are getting on
 - a. Can you remember some? What do you think we are looking at in clinic?

Have we missed anything about your movements that would tell us more about any changes that happen after your treatment?

2. Goal setting
 - a. Do you know why you had the botulinum toxin?
 - b. Do you remember we set some goals for our treatment? (Goals are things we were hoping would improve with your treatment) Do you know what your goals were? Tell me ..have some things changed that you were hoping would?
 - i. All of them..some of them..none of them
 - c. How easy did you find this goal setting to do in clinic....who's goals are they?
 - d. Do you think that you get enough chance to decide these with
 - i. Your mum and dad
 - ii. Your local team
 - iii. The team at GOSH

These interviews will be dependent on age and cognitive ability. The researcher will modify the schedule to encourage the child to express their feelings

- Children will be given the opportunity to use arts and crafts e.g. draw pictures about how they feel before and after injections/Write postcards to a friend / another child about to have injections/Tell stories with Talking Mats

B. The Toxin Study: Interview Schedule for parents



NB Interviews will be more in-depth and will provide parents the opportunity to tell their story and share their views and experiences of their child's life following botulinum toxin injections.

The following prompts will act as guide for the researcher of issues to cover rather than a list of questions to be asked in sequential order.

Today, we are talking about your child's current episode of botulinum toxin injections

- Prompts to answer research question
Are changes dependent on age at time of injection walking ability treatment episode?

2. Is this your child's first injection... If no..... how many have they had before?
 - a. How do they compare?
 - b. Which episode to date has been your child's best response? Why do you think that is?

- Prompts to answer research question
Does stiffness due to dystonia or spasticity change with Botulinum Toxin A injections?

Have you noticed any change in your child's muscles following injections?

4. Are the muscles any looser/stiffer/no change? How would you describe how the muscles have been injected feel? How has it changed since the injections? Is it still changed?
 - a. Has anyone else commented on this? Teachers? Family? Your child?
5. Has your child previously complained of pain in their muscles?
 - a. If yes has this changed after the injections?
 - b. All the time? At night? When?
6. Has your child's energy level changed?
 - a. If yes in what way - can you give examples?

- Prompts to answer research question
Does this make a difference to how your child can function (activity) and join in (participate) with everyday life? Does this influence their quality of life?

How easily does your child get around? How would you describe your child's walking ability to another person?

e.g. community / household/ mostly therapy only?

6. How would you describe your child's movement activities following this set of injections?

Are there things they can do now that they found difficult before?

- a. For example if walking ...change in distance/ease/quality?
- b. Climbing stairs...support required/speed/style

Are there other things that have been made harder for your child? If yes ..what are these?

7. Has there been a change in your child's participation since this last set of injections?

- a. Thinking about activities that they usually do in school? Any changes... for example sit for longer in story time on the mat, getting ready for PE etc.
- b. Out of school e.g. clubs? Any changes....
- c. Anything else?

How do you think the injections have altered any activities /participation? If at all?

8. How happy do you think your child is with the activities they are able to join in with at school?

- a. Do the school adapt activities- how?
- b. Has this changed post toxin?
- c. Have teachers anyone else in the school noticed any change?

9. How happy do you think your child is with the activities they do outside school?

- a. How has this changed post toxin?
- b. Are there opportunities for him /her to join in with friends /siblings? Has this changed following toxin injections?

10. How would you describe your child's quality of life?

- a. Has this changed post injectionif yes when? Still now?
- b. Is it the same..worse..or better ? Why? What are the signs?

Are you still observing the same changes? If not when did it change?

- Prompts to answer research question

Do we measure in clinic what is important for you and your child?

3. In clinic we use a variety of movement tests to capture different parts of your

child's movement abilities.

For example....measuring how their joints move (Joint range), how well they can isolate movement at their joints (selective movement), how strong they are (muscle strength)

We also have some standardised tests looking at walking speed and walking ability , and a test to look at balance, jumping and running

What do you think about what we are measuring?

Is it clear what we are looking at in clinic?

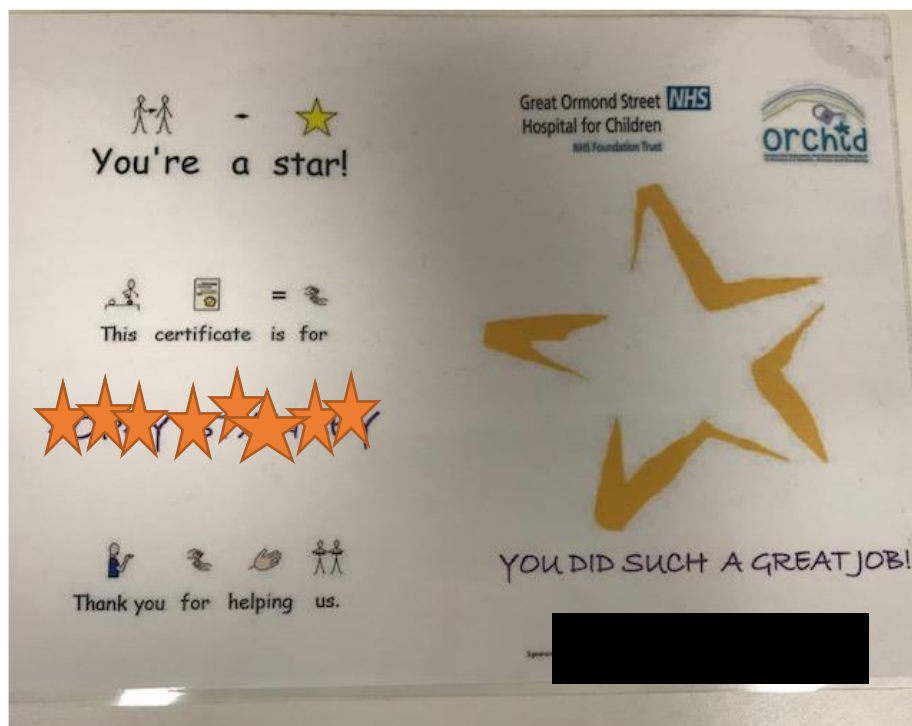
Have we missed anything about your child that would tell us more about any changes they experienced after injections? ... what else would you suggest?

4. Goal setting

- a. Do you know what the goals of treatment were?
- b. Has your child achieved these goals
 - i. All of them..some of them..none of them
- c. How easy or difficult did you find goal setting to do in clinic?
- d. How well do you think that you get the chance to decide these goals with
 - i. Your child, Your local team and The team at GOSH?

Is there anything else you would like to share about your child's Botulinum Toxin treatment?

Example of certificate given to young CYPwCP for participating in Phase II interviews



14.6 COPM Goals

Table shows ICF Coding for Goals set by study participants (n=64)

ICF-CY coding	n
Body structure and function goals	
b280 Sensation of pain	15
Reduce pain during the day	
Reduce pain during the night	
Reduce pain in specific area of body	
Reduce pain during walking	
b455 Exercise tolerance functions	2
Reduce fatigue	
b735 Muscle tone functions	5
Improve ease of stretches	
Reduce scissoring of lower limbs	
b760 Control of voluntary movement functions	4
Improve balance/stability	
b770 Gait pattern functions	36
Improve gait pattern	
Improve foot posture/position	
Improve heel strike during gait	
Straighter legs/ reduce crouch	
b780 Sensations relating to muscles and movement functions	1
Reduce stiffness	
Total BSF Goals	63
Activity & Participation goals	
d410 Changing basic body position	1
Improve ability to get in and out of bath	
d415 Maintaining a body position	3
Improve standing ability/balance	
Improve sitting ability/balance	
d435 Moving objects with lower extremities	4
Kicking a ball	
Improve pedalling/cycling with assistance	
d450 Walking	58
Reduce trips and falls	
Improve walking distance	
Improve walking speed	
Independent walking	
d455 Moving around	8
Improve stair climbing	
Hopping	
Improve cruising	

Improve running	
d460 Moving around in different locations	2
Walking inside independently	
d465 Moving around using equipment	2
Improve walking with walker	
d475 Driving	3
Increase distance when scooting/Riding a bicycle independently	
d530 Toileting	2
Improve independent toileting	
d540 Dressing	7
Improve dressing and changing Putting on trousers independently Putting slippers on foot	
d920 Recreation and leisure	7
Improve swimming Improve fluidity of dancing Improve posture during karate Improve foot posture during ballet	
Total A& P Goals	97
Environmental goals	
e115 Products and technology for personal use in daily living	9
Improve tolerance of splint/Improve tolerance of AFO	
TOTAL	169

14.7 Statistics

14.7.1 Statistics- Normality Tests

BSF

Pain scores Not Normally distributed at any time point

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
pain_score_T0	.317	47	.000	.788	47	.000
pain_score_T1	.296	47	.000	.677	47	.000
pain_score_T2	.372	47	.000	.701	47	.000
pain_score_T3	.304	47	.000	.716	47	.000

Lilliefors Significance Correction

SMC Not Normally distributed at any time point

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
SMC_T0	.213	70	.000	.905	70	.000
SMC_T1	.254	70	.000	.869	70	.000
SMC_T2	.274	70	.000	.851	70	.000
SMC_T3	.287	70	.000	.850	70	.000

a. Lilliefors Significance Correction

Spasticity R1 Gastrocnemius Not Normally distributed except for T2

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
R1_Gastroc_T0	.148	59	.003	.927	59	.002
R1_Gastroc_T1	.109	59	.077	.959	59	.045
R1_Gastroc_T2	.135	59	.009	.976	59	.290
R1_Gastroc_T3	.134	59	.010	.955	59	.029

a. Lilliefors Significance Correction

Spasticity R1 Hamstrings Normally distributed T1 and T3

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HAM_R1_T0	.169	37	.009	.925	37	.016
HAM_R1_T1	.149	37	.037	.967	37	.329
HAM_R1_T2	.189	37	.002	.914	37	.008
HAM_R1_T3	.133	37	.099	.957	37	.166

a. Lilliefors Significance Correction

ACTIVITY

TUG Scores Not Normally distributed at any time point

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
TUG_T0 (s)	.345	48	.000	.417	48	.000
TUG_T1 (s)	.340	48	.000	.538	48	.000
TUG_T2 (s)	.343	48	.000	.490	48	.000
TUG_T3 (s)	.316	48	.000	.514	48	.000

a. Lilliefors Significance Correction

1MFWT – Normally distributed at each time point

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
1MFWT_T0 (m)	.112	48	.178	.980	48	.581
1MFWT_T1 (m)	.107	48	.200*	.956	48	.066
1MFWT_T2 (m)	.115	48	.130	.968	48	.217
1MFWT_T3 (m)	.094	48	.200*	.974	48	.349

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

GMFM -66 – Normally distributed at each time point

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
GMFM66_T0	.063	48	.200*	.973	48	.337
GMFM66_T1	.079	48	.200*	.967	48	.189
GMFM66_T2	.083	48	.200*	.966	48	.178
GMFM66_T3	.078	48	.200*	.954	48	.059

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

QFM Not Normally distributed apart from DM T1 and WS T0

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Align T0	.108	48	.200*	.942	48	.020
Align T1	.150	48	.009	.905	48	.001
Align T2	.171	48	.001	.892	48	.000
Align T3	.138	48	.023	.920	48	.003
Co-ord T0	.140	48	.020	.932	48	.008
Co-ord T1	.147	48	.011	.878	48	.000
Co-ord T2	.176	48	.001	.857	48	.000
Co-ord T3	.177	48	.001	.854	48	.000
Dissoc mov T0	.127	48	.050	.937	48	.013
Dissoc mov T1	.110	48	.196	.953	48	.051
Dissoc mov T2	.127	48	.049	.926	48	.005
Dissoc mov T3	.112	48	.179	.929	48	.006
Stability T0	.097	48	.200*	.944	48	.022
Stability T1	.150	48	.009	.891	48	.000
Stability T2	.188	48	.000	.866	48	.000
Stability T3	.170	48	.001	.870	48	.000
weightshift T0	.098	48	.200*	.955	48	.061
weightshift T1	.128	48	.047	.934	48	.009
weightshift T2	.117	48	.098	.930	48	.007
weightshift T3	.139	48	.021	.945	48	.025

*. This is a lower bound of the true significance.

Goal Setting

COPM-P and COPM-S- Normally distributed at each time point apart from COPM S T0

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
COPM_TOTAL_P_SC ORE_T0	.174	49	.001	.959	49	.086
COPM_TOTAL_P_SC ORE_T1	.104	49	.200*	.985	49	.779
COPM_TOTAL_P_SC ORE_T2	.118	49	.086	.975	49	.391
COPM_TOTAL_P_SC ORE_T3	.072	49	.200*	.977	49	.430
COPM_TOTAL_S_SC ORE_T0	.130	49	.037	.931	49	.006
COPM_TOTAL_S_SC ORE_T1	.120	49	.075	.973	49	.320
COPM_TOTAL_S_SC ORE_T2	.116	49	.095	.959	49	.088
COPM_TOTAL_S_SC ORE_T3	.101	49	.200*	.972	49	.302

*. This is a lower bound of the true significance

a. Lilliefors Significance Correction

CPQOL Normally distributed at all time points

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Feelings_about_funcio ning_T0	.073	49	.200*	.976	49	.397
Feelings_about_funcio ning_T1	.101	49	.200*	.964	49	.138
Feelings_about_funcio ning_T2	.098	49	.200*	.982	49	.665
Feelings_about_funcio ning_T3	.077	49	.200*	.986	49	.832
Participation_and_physi cal_health_T0	.062	49	.200*	.977	49	.434
Participation_and_physi cal_health_T1	.067	49	.200*	.990	49	.955
Participation_and_physi cal_health_T2	.075	49	.200*	.982	49	.658
Participation_and_physi cal_health_T3	.058	49	.200*	.987	49	.872

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

PEM-CY

HOME Frequency and Involvement Not Normally distributed for Average Frequency and involvement at T1 and T3

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HOME_Average_Frequency_(0-7)_T0	.108	47	.200*	.972	47	.324
HOME_Average_Frequency_(0-7)_T1	.148	47	.011	.950	47	.044
HOME_Average_Frequency_(0-7)_T2	.138	47	.026	.952	47	.050
HOME_Average_Frequency_(0-7)_T3	.125	47	.065	.937	47	.014
HOME_Average_Involvement_T0	.134	47	.034	.956	47	.076
HOME_Average_Involvement_T1	.147	47	.013	.935	47	.011
HOME_Average_Involvement_T2	.117	47	.108	.961	47	.122
HOME_Average_Involvement_T3	.168	47	.002	.769	47	.000

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

PEM-CY School Average Frequency Normally distributed Average involvement Not
Normally distributed

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
SCHOOL_Average_Frequency_(0-7)_T0	.091	46	.200 [*]	.977	46	.481
SCHOOL_Average_Frequency_(0-7)_T1	.106	46	.200 [*]	.978	46	.532
SCHOOL_Average_Frequency_(0-7)_T2	.095	46	.200 [*]	.983	46	.725
SCHOOL_Average_Frequency_(0-7)_T3	.075	46	.200 [*]	.967	46	.211
SCHOOL_Average_Involvement_T0	.117	46	.128	.946	46	.034
SCHOOL_Average_Involvement_T1	.136	46	.033	.901	46	.001
SCHOOL_Average_Involvement_T2	.188	46	.000	.882	46	.000
SCHOOL_Average_Involvement_T3	.149	46	.012	.895	46	.001

PEM-CY Community Average Frequency Normally distributed
 Average involvement Not Normally distributed

Tests of Normality

	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
COMM_Average_Frequency _(0-7)_T0	.109	47	.200 [*]	.973	47	.357
COMM_Average_Frequency _(0-7)_T1	.138	47	.025	.982	47	.693
COMM_Average_Frequency _(0-7)_T2	.080	47	.200 [*]	.980	47	.596
COMM_Average_Frequency _(0-7)_T3	.083	47	.200 [*]	.977	47	.469
COMM_Average_Involveme nt_T0	.130	47	.045	.942	47	.022
COMM_Average_Involveme nt_T1	.095	47	.200 [*]	.938	47	.015
COMM_Average_Involveme nt_T2	.149	47	.010	.930	47	.007
COMM_Average_Involveme nt_T3	.097	47	.200 [*]	.934	47	.010

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

14.8.1 Statistics -Non Parametric descriptive data and Tests

Medians (25th and 75th centile) have been presented for all outcomes. A Friedman test was run to determine change in outcome over 12 months following BoNT-A injections. Where this was significant, pairwise comparisons using Wilcoxon rank sum test with continuity correction were performed with a Bonferroni correction for multiple comparisons

Primary outcome measures

QFM (%)	Pre-injection	6 week post injection ***	6 months post injection***	12 months post injection***	Friedmans Test P<0.001
Alignment	56.12 (30.21-77.43)	74.31 (43.76-86.81)	72.46 (43.34-86.69)	77.78 (52.38-86.69)	X ₂ (3) =73.93
Co-ordination	61.02 (36.64-80.73)	72.93 (37.99-90.59)	75.01 (45.59-91.99)	81.69 (45.59-91.99)	X ₂ (3) =79.31
Dissociated Movement	51.99 (29.76-63.94)	56.78 (31.25-71.27)	57.82 (34.96-72.32)	63.1 (42.42-78.21)	X ₂ (3) =47.18
Stability	55.75 (31.35-76.61)	65.76 (36.26-86.00)	70.16 (38.32-84.87)	77.59 (48.39-99.89)	X ₂ (3) =63.11
Weightshift	53.49 (35.12-67.78)	61.81 (36.30-75.80)	64.04 (43.19-77.52)	67.5 (48.94-79.44)	X ₂ (3) =82.98

Median (25th and 75th centile) All results T1-T3 for all attributes significant following Bonferroni correction p<.001***

COPM	Pre-injection	6 week post injection	6 months post injection	12 months post injection	Friedmans Test
COPM Performance (1-10)	3 (2.67-4.38)	6.17 (4.46-7.08)***	5 (4-6.5)***	5.67 (4.5-7.33)**	$\chi^2 (3) = 73.64$ $p < .001$
COPM Satisfaction (1-10)	3 (2-4)	5.67 (4.46-7.5)***	4.75 (3.42-7)***	5.67 (4.33-7.5)***	$\chi^2 (3) = 66.98$ $p < .001$

Median (25th and 75th centile) Pairwise comparison following Bonferroni correction, significant change from baseline $p < 0.05$ * $P < 0.01$ **, $p < 0.001$ ***

Secondary outcome measures

BSF	Pre-injection	6 week post injection	6 months post injection	12 months post injection	Friedmans Test
SMC (0-4)	2 (1-3)	3 (2-3)	3 (2-4)*	3 (2-4)**	$X_2(3) = 34.01$ $p < .001$
R1 Gastrocnemius muscle (°)	-20 (-20,-10)	-10 (-20,-5)***	-15 (-20,-10)	-15 (-20,-10)	$X_2(3) = 36.72$ $p < .001$
MAS Gastrocnemius (0-5)	3 (3,4)	2 (1.75,3)***	3 (2,4)	3 (2,3)	$\chi^2(3) = 24.48$, $p < .001$
R1 Hamstring muscle (°)	85 (70-90)	65 (60-70)***	75 (65-85)*	75 (60-87.5)*	$X_2(3) = 24.48$ $p < .001$
MAS Hamstrings (0-5)	3 (3,3)	2 (1,2) ***	2(1,3) ***	2 (1,3)***	$\chi^2(3) = 36.72$ $p < .001$

Median (25th and 75th centile) Pairwise comparison significance following Bonferroni correction $p < 0.05$ * $P < 0.01$ ** , $p < 0.001$ ***

ACTIVITY	Pre-injection	6 week post injection	6 months post injection	12 months post injection	Friedmans Test
1 MFWT (metres)	62.5 (46.5-81)	68.5 (47.25-87.75)	69.0 (47.25-81.00)	72.0 (52.00-91.00)*	$X_2(3) = 12.26$ $p < 0.01$
TUG (seconds)	6.23 (4.68-9.30)	5.80 (4.79-8.54)	5.07 (4.16-7.39)**	4.74 (3.98-7.2)***	$X_2(3) = 33.94$ $p < .001$
GMFM-66 (%)	71.46 (63.98-81.93)	74.19 (66.07-81.93)***	76.15 (65.89-83.55)***	79.99 (68.86-89.7)***	$X_2(3) = 65.78$ $p < .001$

Median (25th and 75th centile) Pairwise comparison significance following Bonferroni correction $p < 0.05$ * $P < 0.01$ ** , $p < 0.001$ ***

Participation	Pre-injection	6 week post injection	6 months post injection	12 months post injection	Friedmans Test
CPQOL Function (%)	67.71 (60.16-75.26)	72.92 (66.41-83.85)**	71.88 (65.63-80.47)*	72.92 (64.06-79.43)**	$X_2(3) = 17.47$ $p = 0.001$
CPQOL Participation(%)	56.82 (41.76-66.19)	64.20 (50.85-75)	64.77 (55.40-73.86)**	63.63(55.68-73.30)**	$X_2(3) = 17.52$ $p = 0.001$
PEMCY Home Average Frequency (0-7)	5.45 (5-6)	5.9 (5.2-6.2)*	5.9(5.15-6.35)***	5.8 (5.25-6.3)**	$X_2(3) = 20.62$ $p < 0.001$
PEMCY Home Average Involvement (0-5)	3.95(3.5-4.26)	4.21 (3.78-4.5)**	4.2 (3.75-4.5)**	4.13 (3.87-4.5)***	$X_2(3) = 24.62$ $p < 0.001$
PEMCY School Average Frequency (0-7)	3.6 (3-4.5)	4 (3.2-4.6)	4.2 (3.4-5)	4.2 (3.2-5)	$X_2(3) = 4.57$ $p = 0.206$
PEMCY School Average Involvement (0-5)	4 (3.25-4.75)	4.33 (3.53-5)	3.9 (3.53-5)*	4.2 (3.75-4.95)*	$X_2(3) = 14.37$ $p = 0.002$
PEMCY Community Average Frequency (0-7)	2.4 (1.9-3.03)	2.6 (2.3-3.6)	2.8 (2.2-3.3)*	2.7 (2.2-3.48)	$X_2(3) = 10.27$ $p = 0.016$
PEMCY Community Average Involvement (0-5)	4.13 (3.54-4.5)	4.25 (3.72-4.71)	4.14 (3.61-4.5)	4.3 (3.69-4.73)	$X_2(3) = 9.12$ $p = 0.028$

Median (25th and 75th centile) Pairwise comparison significance following Bonferroni correction $p < 0.05$ * $P < 0.01$ ** , $p < 0.001$ ***

14.8.2 Statistics- Mann Whitney U Tests Missing Data Analyses

ACTIVITY Measures Missing Data

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of TUG_T0 (s) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.151	Retain the null hypothesis.
2	The distribution of TUG_T1 (s) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.128	Retain the null hypothesis.
3	The distribution of TUG_T2 (s) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.092	Retain the null hypothesis.
4	The distribution of TUG_T3 (s) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.467 ^c	Retain the null hypothesis.
5	The distribution of 1MFWT_T0 (m) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.445	Retain the null hypothesis.
6	The distribution of 1MFWT_T1 (m) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.149	Retain the null hypothesis.
7	The distribution of 1MFWT_T2 (m) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.142	Retain the null hypothesis.
8	The distribution of 1MFWT_T3 (m) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.254 ^c	Retain the null hypothesis.
9	The distribution of GMFM D (/39) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.696	Retain the null hypothesis.
10	The distribution of GMFM E (/72) is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.342	Retain the null hypothesis.

11	The distribution of GMFM66_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.638	Retain the null hypothesis.
12	The distribution of GMFM66_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.135	Retain the null hypothesis.
13	The distribution of GMFM66_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.077	Retain the null hypothesis.
14	The distribution of GMFM66_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.181 ^c	Retain the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

c. Exact significance is displayed for this test.

Pain and COPM

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of pain_score_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.786	Retain the null hypothesis.
2	The distribution of pain_score_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.123	Retain the null hypothesis.
3	The distribution of pain_score_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.451 ^c	Retain the null hypothesis.
4	The distribution of pain_score_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.418 ^c	Retain the null hypothesis.

5	The distribution of COPM_TOTAL_P_SCORE_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.424	Retain the null hypothesis.
6	The distribution of COPM_TOTAL_P_SCORE_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.945	Retain the null hypothesis.
7	The distribution of COPM_TOTAL_P_SCORE_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.968	Retain the null hypothesis.
8	The distribution of COPM_TOTAL_P_SCORE_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.784 ^c	Retain the null hypothesis.
9	The distribution of COPM_TOTAL_S_SCORE_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.547	Retain the null hypothesis.
10	The distribution of COPM_TOTAL_S_SCORE_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.897	Retain the null hypothesis.
11	The distribution of COPM_TOTAL_S_SCORE_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.848	Retain the null hypothesis.
12	The distribution of COPM_TOTAL_S_SCORE_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.803 ^c	Retain the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

c. Exact significance is displayed for this test.

QFM

Hypothesis Test Summary

Null Hypothesis	Test	Sig. ^{a,b}	Decision
-----------------	------	---------------------	----------

1	The distribution of Align T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.586	Retain the null hypothesis.
2	The distribution of Align T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.086	Retain the null hypothesis.
3	The distribution of Align T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.134	Retain the null hypothesis.
4	The distribution of Align T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.058 ^c	Retain the null hypothesis.
5	The distribution of Co-ord T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.808	Retain the null hypothesis.
6	The distribution of Co-ord T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.205	Retain the null hypothesis.
7	The distribution of Co-ord T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.051	Retain the null hypothesis.
8	The distribution of Co-ord T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.207 ^c	Retain the null hypothesis.
9	The distribution of Dissoc mov T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.649	Retain the null hypothesis.
10	The distribution of Dissoc mov T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.294	Retain the null hypothesis.
11	The distribution of Dissoc mov T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.124	Retain the null hypothesis.
12	The distribution of Dissoc mov T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.082 ^c	Retain the null hypothesis.
13	The distribution of Stability T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.833	Retain the null hypothesis.
14	The distribution of Stability T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.181	Retain the null hypothesis.

15	The distribution of Stability T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.054	Retain the null hypothesis.
16	The distribution of Stability T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.234 ^c	Retain the null hypothesis.
17	The distribution of weightshift T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.739	Retain the null hypothesis.
18	The distribution of weightshift T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.162	Retain the null hypothesis.
19	The distribution of weightshift T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.054	Retain the null hypothesis
20	The distribution of weightshift T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.144 ^c	Retain the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

c. Exact significance is displayed for this test.

CPQOL

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of Feelings_about_functioning_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.795	Retain the null hypothesis.
2	The distribution of Feelings_about_functioning_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.547	Retain the null hypothesis.

3	The distribution of Feelings_about_functioning_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.207	Retain the null hypothesis.
4	The distribution of Feelings_about_functioning_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.439	Retain the null hypothesis.
5	The distribution of Participation_and_physical_health_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.495	Retain the null hypothesis.
6	The distribution of Participation_and_physical_health_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.247	Retain the null hypothesis.
7	The distribution of Participation_and_physical_health_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.411	Retain the null hypothesis.
8	The distribution of Participation_and_physical_health_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.059	Retain the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

PEM-CY

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of HOME_Average_Frequency_(0-7)_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.553	Retain the null hypothesis.
2	The distribution of HOME_Average_Frequency_(0-7)_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.075	Retain the null hypothesis.

3	The distribution of HOME_Average_Frequency_(0-7)_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.396	Retain the null hypothesis.
4	The distribution of HOME_Average_Frequency_(0-7)_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.302 ^c	Retain the null hypothesis.
5	The distribution of HOME_Average_Involvement_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.697	Retain the null hypothesis.
6	The distribution of HOME_Average_Involvement_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.328	Retain the null hypothesis.
7	The distribution of HOME_Average_Involvement_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.606	Retain the null hypothesis.
8	The distribution of HOME_Average_Involvement_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.392 ^c	Retain the null hypothesis.
9	The distribution of SCHOOL_Average_Frequency_(0-7)_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.625	Retain the null hypothesis.
10	The distribution of SCHOOL_Average_Frequency_(0-7)_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.866	Retain the null hypothesis.
11	The distribution of SCHOOL_Average_Frequency_(0-7)_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.773	Retain the null hypothesis.
12	The distribution of SCHOOL_Average_Frequency_(0-7)_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.193 ^c	Retain the null hypothesis.

13	The distribution of SCHOOL_Average_Involvement_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.096	Retain the null hypothesis.
14	The distribution of SCHOOL_Average_Involvement_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.497	Retain the null hypothesis.
15	The distribution of SCHOOL_Average_Involvement_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.532	Retain the null hypothesis.
16	The distribution of SCHOOL_Average_Involvement_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.203 ^c	Retain the null hypothesis.
17	The distribution of COMM_Average_Frequency_(0-7)_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.321	Retain the null hypothesis.
18	The distribution of COMM_Average_Frequency_(0-7)_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.557	Retain the null hypothesis.
19	The distribution of COMM_Average_Frequency_(0-7)_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.919	Retain the null hypothesis.
20	The distribution of COMM_Average_Frequency_(0-7)_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.290 ^c	Retain the null hypothesis.
21	The distribution of COMM_Average_Involvement_T0 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.987	Retain the null hypothesis.
22	The distribution of COMM_Average_Involvement_T1 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.496	Retain the null hypothesis.

23	The distribution of COMM_Average_Involvement_T2 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.738	Retain the null hypothesis.
24	The distribution of COMM_Average_Involvement_T3 is the same across categories of Data status.	Independent-Samples Mann-Whitney U Test	.853 ^c	Retain the null hypothesis.

- a. The significance level is .050.
- b. Asymptotic significance is displayed.
- c. Exact significance is displayed for this test.

R1 Gastrocnemius

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of R1_Gastroc_T0 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.929	Retain the null hypothesis.
2	The distribution of R1_Gastroc_T1 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.825	Retain the null hypothesis.
3	The distribution of R1_Gastroc_T2 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.704	Retain the null hypothesis.
4	The distribution of R1_Gastroc_T3 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.469	Retain the null hypothesis.

- a. The significance level is .050.
- b. Asymptotic significance is displayed.

R1 Hamstrings

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	
1	The distribution of HAM_R1_T0 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.003 ^c	Reject the
2	The distribution of HAM_R1_T1 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.038 ^c	Reject the
3	The distribution of HAM_R1_T2 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.026 ^c	Reject the
4	The distribution of HAM_R1_T3 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.043 ^c	Reject the

a. The significance level is .050.

b. Asymptotic significance is displayed.

c. Exact significance is displayed for this test.

Summary

A Mann-Whitney U test was run to determine if there were differences in *MTS R1 for Hamstrings* score between complete (n=37) and missing (n=6) data sets across assessment time points. Distributions of the R1 scores for data sets were not similar, as assessed by visual inspection. R1 scores for missing (mean rank = 35.25) were statistically significantly higher than for complete (mean rank = 19.85) at baseline, $U = 190.5$, $z = 2.82$, $p = .01$.

T1 missing n=6 (mean rank 31.75) vs complete n=37 (mean rank 20.42) $U = 169.5$, $z = 2.07$, $p = .04$

T2 missing n=4 (mean rank 33.50) vs complete n=37(mean rank 19.65) $U = 124$, $z = 2.22$, $p = .03$

T3 missing n=2 (mean rank 35.25) vs complete n=37(mean rank 19.18) $U = 67.5$ $z = 1.95$, $p = .04$

However only 3 missing data sets had hamstrings injections and two of these had orthopaedic surgery by T3

1 child with Bilateral Hamstring missed T2 (2 hamstring injections)

2 children with Bilateral injections missed T3 (4 hamstring injections)

Numbers are too small to do statistical testing and draw conclusions

SMC

Hypothesis Test Summary

	Null Hypothesis	Test	Sig. ^{a,b}	Decision
1	The distribution of SMC_T0 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.931	Retain the null hypothesis.
2	The distribution of SMC_T1 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.131	Retain the null hypothesis.
3	The distribution of SMC_T2 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.517	Retain the null hypothesis.
4	The distribution of SMC_T3 is the same across categories of missing_data.	Independent-Samples Mann-Whitney U Test	.172	Retain the null hypothesis.

a. The significance level is .050.

b. Asymptotic significance is displayed.

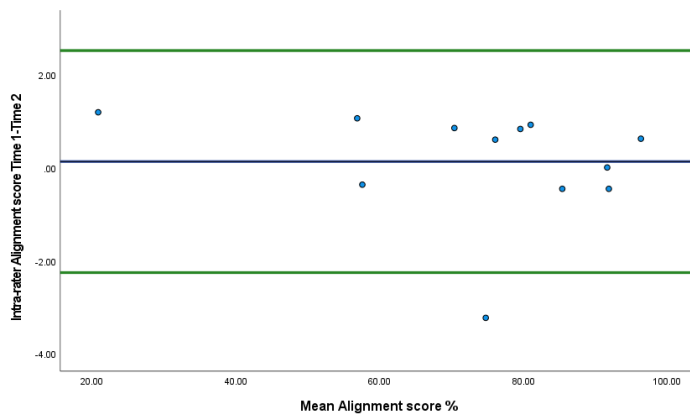
14.8.3 Statistics- QFM Intra-rater reliability

Intra-rater Paired samples T-Tests comparing QFM attribute scores

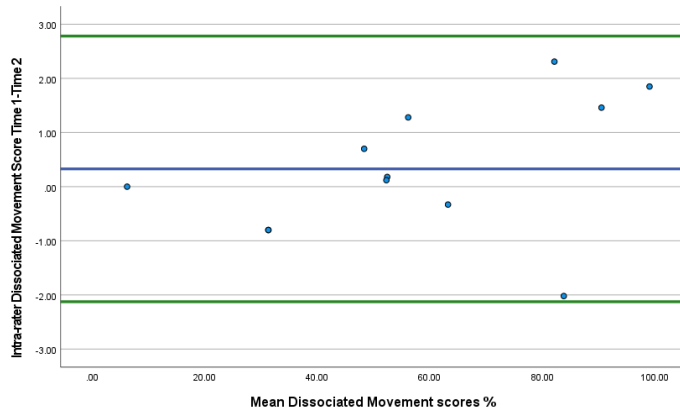
QFM attribute	t	df	Significance. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Alignment	.364	11	.723	.12833	-.6475	.9042
Co-ordination	-.048	11	.963	-.01667	-.7886	.7553
Dissociated Movement	.911	11	.382	.32917	-.4661	1.1245
Stability	-1.615	11	.135	-.28000	-.6616	.1016
Weight shift	.826	11	.426	.21750	-.3617	.7967

Intra-rater agreement Bland-Altman tests and plots

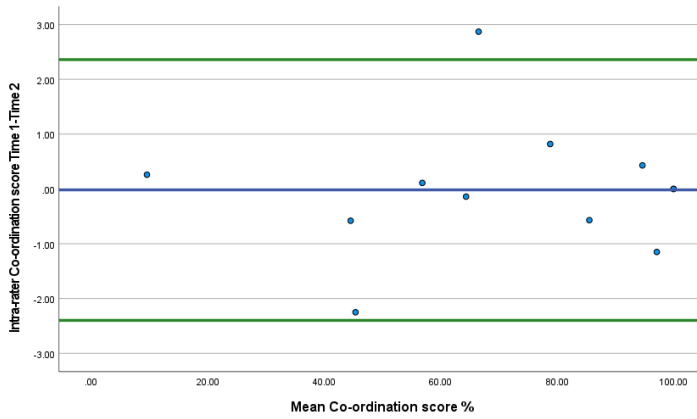
	Mean difference between ratings	SD of difference Between ratings	95% LOA (%)
Alignment	0.13	1.22	-2.26-2.52
Coordination	0.16	1.21	-2.37-2.78
Dissociated movement	0.33	1.25	-2.78-2.12
Stability	0.28	0.60	-1.45-0.90
Weight-shift	0.22	0.91	-1.57-2.04



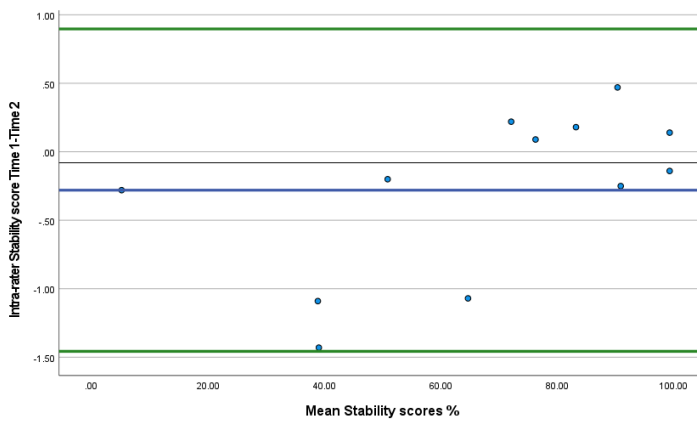
- Bland-Altman plot for intra-rater Alignment scores



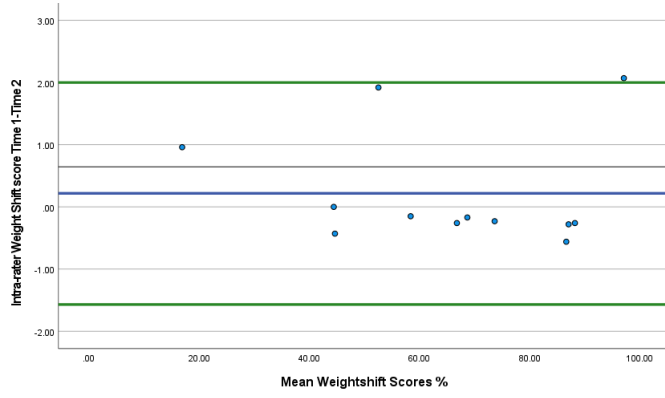
- Bland-Altman plot for intra-rater Dissociated Movement scores



Bland-Altman plot for intra-rater Co-ordination scores



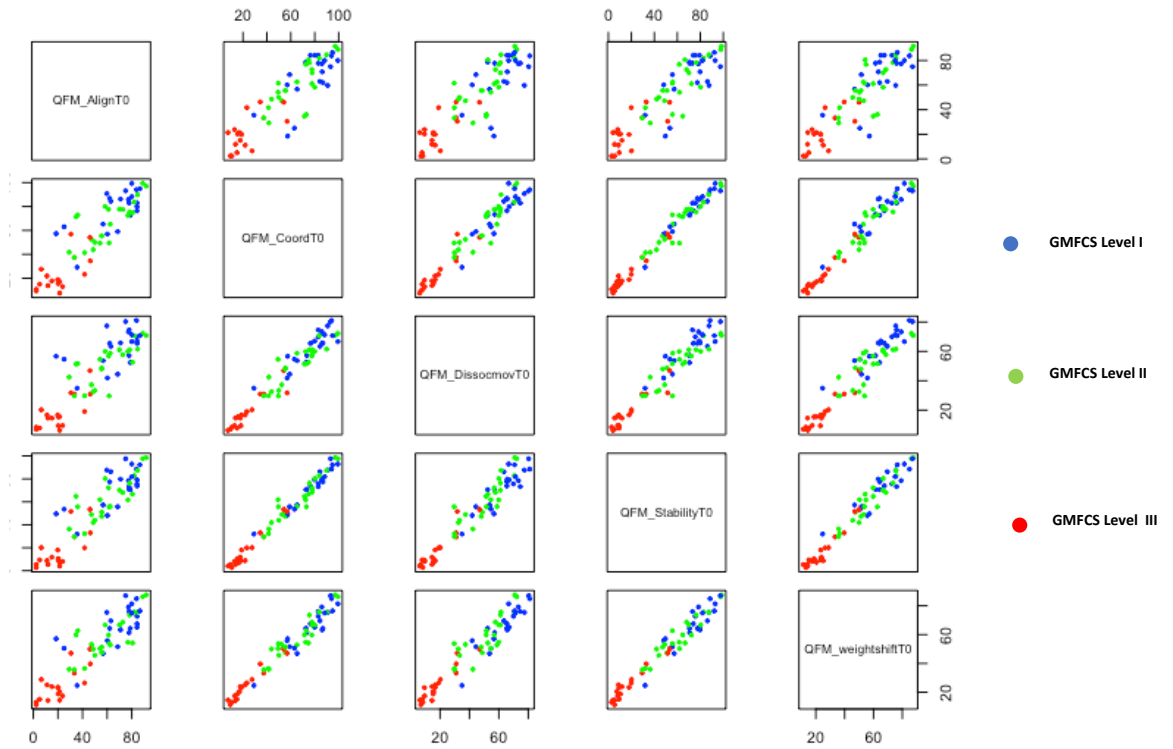
Bland-Altman plot for intra-rater Stability scores



Bland-Altman plot for intra-rater Weightshift scores

14.8.4 Statistics -QFM Correlation

T0 - Baseline Pre- BoNT-A

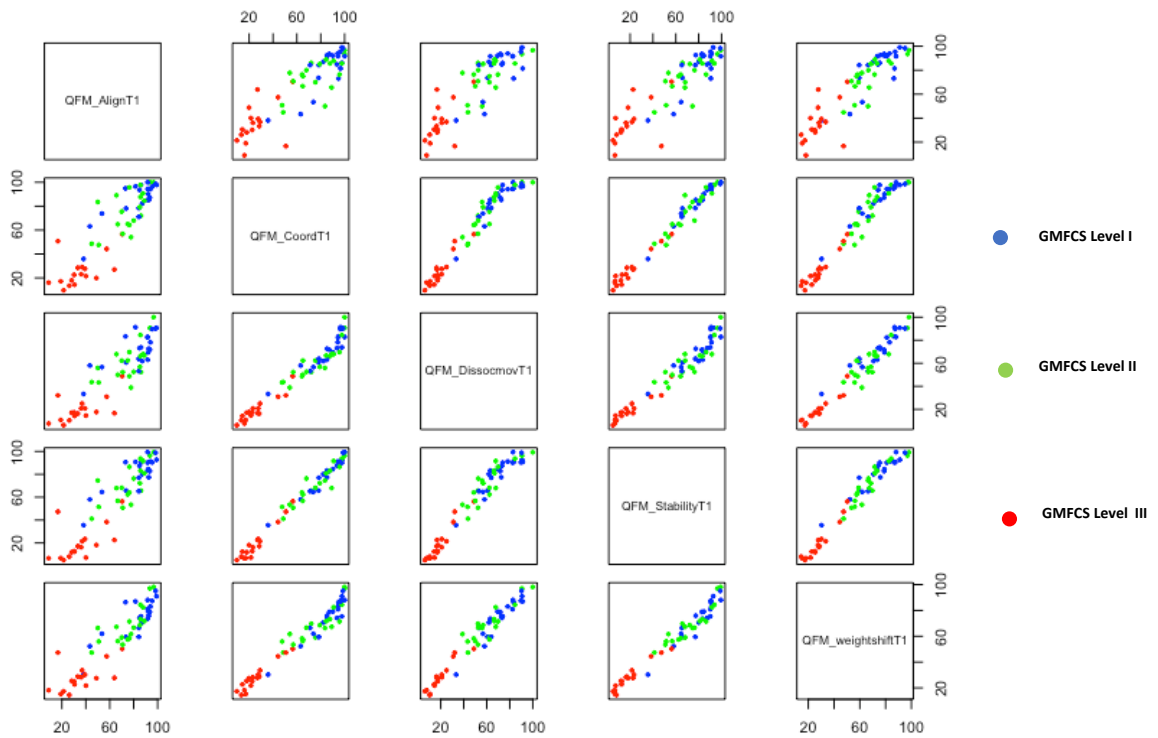


Scatter plot matrices showing correlation of QFM attributes at baseline T0

QFM Baseline T0 Correlation coefficients (Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Coordination	0.88 (0.81-0.93)			
Dissociated Movement	0.86 (0.78-0.91)	0.97 (0.95-0.98)		
Stability	0.90 (0.84-0.94)	0.99 (0.98-0.99)	0.96 (0.94-0.98)	
Weightshift	0.89 (0.82-0.93)	0.98 (0.96-0.99)	0.95 (0.92-0.97)	0.98 (0.96-0.99)

Pearson correlation for QFM attribute scores at baseline

T1- 6 weeks post BoNT-A

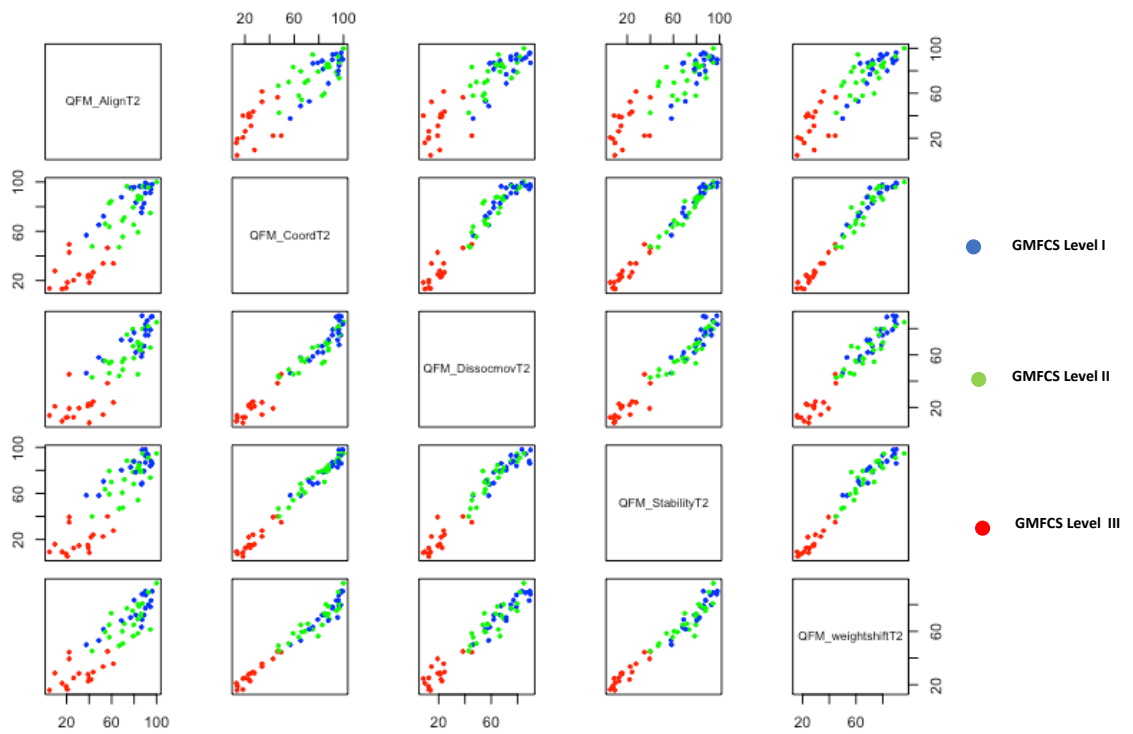


Scatter plot matrices showing correlation of QFM attributes at 6 weeks post BoNT-A

QFM T1 Correlation coefficients (Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Coordination	0.88 (0.81-0.93)			
Dissociated Movement	0.88 (0.8-0.92)	0.97 (0.95-0.98)		
Stability	0.90 (0.84-0.94)	0.99 (0.98-0.99)	0.97 (0.95-0.98)	
Weightshift	0.90 (0.84-0.94)	0.97 (0.96-0.98)	0.97 (0.95-0.98)	0.98 (0.97-0.99)

Pearson correlation for QFM attribute scores at 6 weeks post BoNT-A

T2- 6 months post BoNT-A



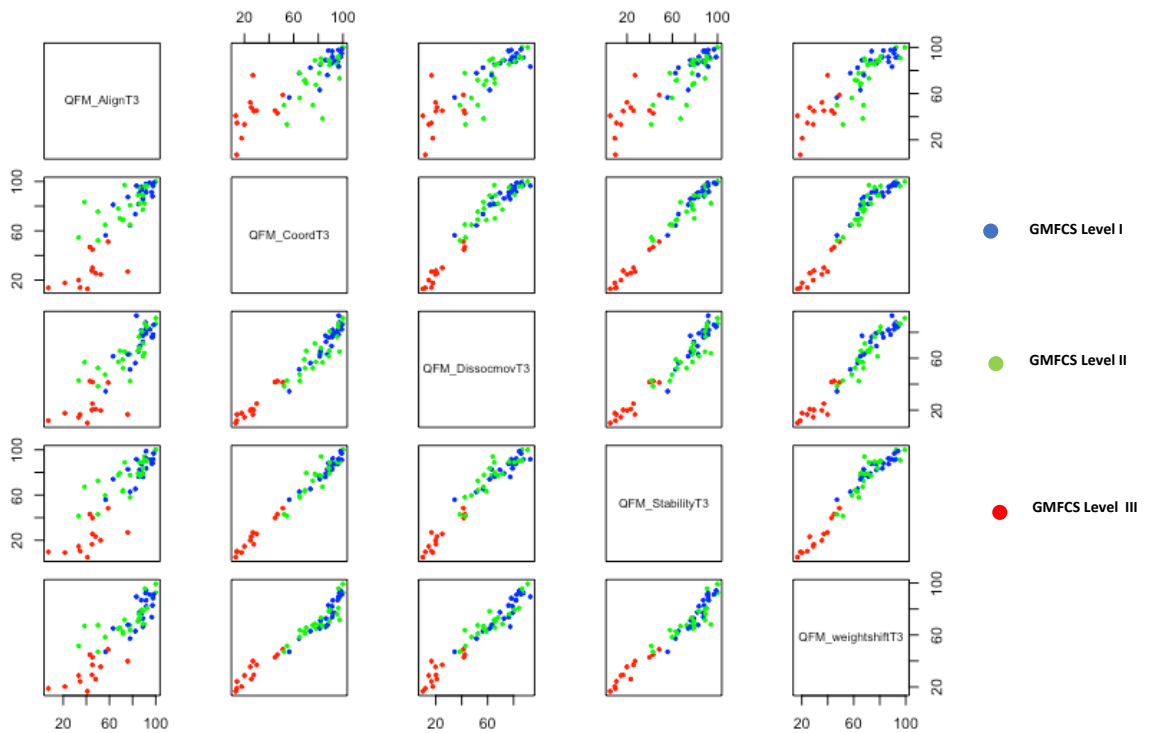
Scatter plot matrices showing correlation of QFM attributes at **6 months** post BoNT-

A

QFM T2 Correlation coefficients (Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Coordination	0.88 (0.81-0.93)			
Dissociated Movement	0.88 (0.81-0.93)	0.97 (0.95-0.98)		
Stability	0.88 (0.81-0.93)	0.99 (0.98-0.99)	0.97 (0.95-0.98)	
Weightshift	0.89 (0.83-0.94)	0.98 (0.97-0.99)	0.97 (0.95-0.98)	0.98 (0.96-0.99)

Pearson correlation for QFM attribute scores at **6 months** post BoNT-A

T3- 12 months post BoNT-A



Scatter plot matrices showing correlation of QFM attributes at 12 months post BoNT-A

QFM T3 Correlation coefficients (Confidence Interval)	Alignment	Coordination	Dissociated Movement	Stability
Coordination	0.85 (0.76-0.91)			
Dissociated Movement	0.86 (0.78-0.92)	0.97 (0.94-0.98)		
Stability	0.88 (0.8-0.93)	0.99 (0.98-0.99)	0.96 (0.94-0.98)	
Weightshift	0.88 (0.8-0.93)	0.97 (0.95-0.98)	0.97 (0.95-0.98)	0.98 (0.94-0.98)

Pearson correlation for QFM attribute scores at **12 months** post BoNT-A

14.8.5 Statistics – Multilevel Regression: The Bayesian Information Criterion

The Bayesian Information Criterion (BIC)	Null	Time	Time + all confounders
ACTIVITY			
QFM alignment	2021.008	1898.079	1825.726
QFM coordination	1867.445	1759.052	1652.327
QFM dissociated movement	1848.762	1763.805	1649.569
QFM stability	1878.625	1788.213	1676.49
QFM weight shift	1812.505	1690.988	1592.639
1MFWT	1985.8	1983.629	1901.625
TUG	1647.917	1651.154	1617.744
GMFM66	1517.552	1446.826	1366.905
IMPAIRMENT			
SMC	793.4498	777.1914	777.9102
R1 hamstrings	1399.573	1350.742	1324.895
R1 gastrocnemius	2000.66	1982.752	1988.773
PARTICIPATION			
COPM-performance	1027.42	938.3416	971.6798
COPM-satisfaction	1095.866	1018.133	1049.899
CPQOL function	1794.776	1775.345	1777.718
CPQOL participation	1943.032	1921.101	1918.825
PEM-CY Home average Frequency	434.6362	439.3713	492.3657
PEM-CY Home average involvement	363.5901	373.2142	432.211
PEM-CY School average frequency	646.4382	659.0284	703.7394
PEM-CY school average involvement	465.5846	483.6491	534.9286
PEM-CY Community average frequency	559.4301	572.8334	618.3459
PEM-CY Community average involvement	421.468	438.4303	494.673
Best fit/Exceeds null model/No apparent relationship			

14.9 Systematic Review

14.9.1 Systematic review -PROSPERO protocol

What are the effects of lower limb botulinum toxin A injections on activity, participation and quality of life in ambulant children with cerebral palsy?

Lesley Katchburian, Xanthe Hodgson, Deepti Chugh, Jo Wray, Belinda Crowe, Joanna Coghill, Kate Oulton Lucinda Carr

PROSPERO 2019 CRD42019138523 Available

from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019138523

Review question

BoNT-A is already established as an effective antispasticity treatment in the management of children and young people with Cerebral Palsy (CYPwCP). However there is little evidence to confirm that any improvement seen at impairment level results in a change in activity, participation or quality of life (QOL) in this population.

This systematic review will consider the impact of lower limb BoNT-A injections on activity, participation and quality of life in ambulant CYPwCP defined as Gross Motor Function Classification System (GMFCS) levels IIII

Searches

Six electronic databases will be searched: Scopus, CINAHL, MEDLINE, EMBASE, Cochrane Library, Web of Science from a publication date from 2007.

Additional searches will be carried out in the grey literature and from abstracts from conference proceedings including; American Academy for Cerebral Palsy and Developmental Medicine, European Academy of Childhood Disability and Australasian Academy for Cerebral Palsy and Developmental Medicine. Studies will be included if they are published in the English language.

Types of study to be included

Original trials evaluating the effects of BoNT-A injections into the lower limb muscles of ambulant CYPwCP within the three domains of the World Health Organization's International Classification of Functioning, Disability and Health - Children and Youth Model ICF-CY (body structure and functions, activity and participation) (WHO 2007). Including; randomized controlled trials; quasi-randomized controlled trials; prospective pre-post studies and cohort studies with a concurrent control group. Studies should have a minimum of ten participants (n?10). Systematic reviews and meta-analyses will be excluded but searched to ensure relevant articles are identified. Articles will be excluded if they are reviews, letters, conference abstracts or commentaries.

Condition or domain being studied

Children and Young People with Cerebral Palsy (CP). This is "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain"(Bax et al.2005). The motor disorders of CP are often accompanied by "disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and secondary musculoskeletal problems ". CP is the most common physical neurodisability of childhood and is the greatest cause of referral to rehabilitation services than any other paediatric diagnosis (Odding et al., 2006). It has a life-long impact on children and young people and families, with a prevalence of 2-3 per 1000 live births throughout Europe and 110, 000 affected individuals in the UK.

Participants/population

Inclusion Criteria:

Children between 2 and 18 years

- Confirmed diagnosis of ambulant CP (GMFCS level I-III)
- Lower limb intra-muscular Botulinum Toxin A administration (alone or in combination with additional therapy).
- Original clinical trials (n ≥10) measuring the therapeutic effect of BoNT-A
- Therapeutic effect post BoNT-A must include outcomes of activity and participation in addition to impairment outcome
- Full text publication in English

Exclusion Criteria:

- Participants without CP
- Failure to describe the ambulatory level of the study participants (currently described as GMFCS level I-III).
- Studies with participants from all GMFCS Levels I-V if relevant data from GMFCS level I-III could not be separated.
- Upper limb BoNT-A only (relevant data from studies with participants of mixed upper and lower limb injections where results from lower limb injections could not be separated)
- Studies investigating effects of BoNT-A for non-motor problems (e.g. drooling or bladder instability)
- Studies without measurement of therapeutic outcome of BoNT-A (e.g. describing pathophysiology, or administration techniques and side effects profiles)
- No full text available, abstract-only articles (books, conference, letters), systematic review and meta analysis.
- Results reported at less than 4 weeks post BoNT-A injection
- Full text not available in English.

Intervention(s), exposure(s)

Lower limb intramuscular injections of Botulinum neurotoxin A (BoNT-A) to children and young people with ambulant cerebral palsy.

Comparator(s)/control

Comparators of interest in this review are:

- No intervention
- Standard or usual care
- Additional physical therapy such as casting, functional electrical stimulation or training programs

Context

Main outcome(s)

Studies will be included if they report continuous outcome related to the ICF domains of body functions activity limitations and participation restriction. Outcomes should be evaluated using a valid or clinically accepted measure for CYPwCP.

Timing and effect measures

Studies will be included if the length of follow up after BoNT-A administration exceeds 4 weeks. This will ensure that clinical effects of BoNT-A will be manifest.

Additional outcome(s)

None

Timing and effect measures

Not applicable.

Data extraction (selection and coding)

Two reviewers (LK/LC) will screen titles and abstracts of articles to identify articles for inclusion using the predefined eligibility criteria. Reference lists of included articles will be reviewed for supplementary literature not identified using the search strategy. Backward and forward citation chasing will be carried out to help confirm the saturation of the initial searches. Each step of the selection process will be captured in a PRISMA-style flow chart.

Full text articles meeting inclusion criteria will be retrieved and reviewed in full by the reviewers. If necessary, the study authors will be contacted for clarification and additional information to inform study selection.

Summary data of each included article will be extracted independently into a data extraction form specifically designed for this review. If there is a study with more than one publication, then reports will be compared and the publication with the most complete data will be used. Discrepancies between different versions will be highlighted. Disparities will be resolved by discussion and consultation with the review team and if there is still disagreement, this will be arbitrated by an independent expert.

Microsoft Excel data extraction tables will be used to record details of methodological quality as well as the following descriptive details:

1. Participants: study setting; study population and participant characteristics;
2. Study: date of publication; country of origin; sample size; study type; length of study.
3. Intervention; BoNT-A type (BOTOX, Dysport etc.), dose-including dilution details, administration (e.g. ultrasound guidance), safety outcomes, sedation protocols, no of injections, injection frequency, including toxin naive or repeat injection, muscles injected.
4. Outcome measures used: domains/dimensions of ICF; number of items; description of the items; response method; method of administration; psychometric properties (including floor or ceiling effects).
5. Outcome of efficacy of BoNT-A as related to domains of ICF, interpretation and summary scoring.

Risk of bias (quality) assessment

Two reviewers (LK/LC) will assess the quality of the studies independently without blinding to authorship or journal conducting 'Risk of Bias' and Quality assessments using AACPDM framework. Discrepancies will be resolved by discussion in conjunction with the review team.

Strategy for data synthesis

We will provide a narrative synthesis of the findings from the included studies, structured around the range of outcome measures used and documented efficacy. In addition we will analyse baseline characteristics of impairment, activity, participation and QOL. We will provide summaries of intervention effects of BoNT-A with standardised mean differences for continuous outcomes. We anticipate that there will be limited scope for meta-analysis because of the wide range of different outcomes measured across the existing studies. However, where studies have used the same type of intervention and comparator, with the same outcome measures, we will pool the results using a random effects meta-analysis, with standardised mean differences for continuous outcomes and calculate 95% confidence intervals and two sided P values for each outcome.

Analysis of subgroups or subsets

Subgroup analysis will be used to investigate the effect of BoNT- A in all ICF Domains.

Contact details for further information

Lesley Katchburian

lesley.katchburian@gosh.nhs.uk

14.9.2 Systematic Review-Medline Search

Ovid MEDLINE(R) ALL <1946 to July 15, 2022>

- 1 Cerebral Palsy/ 22829
- 2 Dystonia/ 7044
- 3 exp Muscle Hypertonia/ 13127
- 4 hemiplegia/ or quadriplegia/ 19941
- 5 (cerebral pals* or spasticity or dystonia* or hypertonia* or increased tone or diplegia or quadriplegia or hemiplegia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 88159
- 6 1 or 2 or 3 or 4 or 5 90195
- 7 exp Botulinum Toxins/ 17957
- 8 ((botulinum toxin adj2 A) or (BTX adj2 A) or BTX or (BONT adj2 A) or (botulinum neurotoxin adj2 a) or BTA or BTXA or BOTOX or DYSPORT or XEOMIN or INCOBOTULINUM TOXIN A or ONABOTULINUM TOXIN or ABOBOBOTULINUM TOXIN A or NEURONOX).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 14337
- 9 7 or 8 23188
- 10 6 and 93932
- 11 limit 10 to "all child (0 to 18 years)" 1034

14.9.3 Data Extraction Form- instructions for reviewers

PART 1: REVIEW, REVIEWER AND STUDY INFORMATION

Study ID

Reviewer Name

Date of completion of Form

Title of Article

Author

Source Details (year of publication, journal, vol, page no)

Type of Report (eg full paper/abstract)

PART 2: STUDY ELIGIBILITY

Type of STUDY Design

(RCT, controlled before and after, observational etc..)

Participants in Study classified as ambulant GMFCS I-III

or equivalent descriptor(NB ≥ 10 participants)

Yes/No/Unclear

Lower Limb BoNT-A only

Yes/No/Unclear

BoNT-A intervention

Details of Dose dilution administration details sedation

BoNT-A frequency- ie no of previous injections Toxin naive/ Note how many injection episodes within the study period

Comparison group

casting/strengthening/ change in therapy intensity type etc

Yes/No/Unclear

Outcomes in Impairment/Activity/Participation

(+/- QOL or Satisfaction measure)

Yes/No/Unclear

If you have answered NO to any of the questions about participants, interventions or outcomes please STOP here

If there is no comparison group or you have answered YES to ALL questions, please proceed to Part 3

PART 3: INFORMATION ABOUT THE STUDY

Characteristics of the Study

Country study conducted

Source of Funding

Date study undertaken (data collection)

Number of participating centres

Characteristics of the Participants:

Inclusion & Exclusion criteria

Number of potential participants (i.e. approached for inclusion)

Number who did participate

Number of participants at baseline

Number of participants not followed up and reasons

Type of comparison group eg intervention casting+

Intervention group

Duration of Follow up

Age range of participants (range, mean, S.D)

Gender number % female vs male

GMFCS levels number, %

Number of previous injections (or toxin naive) prior to study

Comparison group (if applicable):

Duration of Follow up

Age range of participants (range, mean, S.D)

Gender number % female vs male

GMFCS levels number, %

Number of previous injections (or toxin naive) prior to study

Characteristics of BoNT-A intervention

Product/ dose total and per muscle (including dilution)

Administration details (who injected/setting –where/ sedation used)

BoNT-A frequency (single or multiple injections in study period)

Muscle groups injected

% of children with multiple muscle groups injected

Concurrent Therapy interventions post BoNT-A INTERVENTION group (eg PT/Orthotics /Casting/ other..)

Physiotherapy: (Details of frequency/ content/ dosage/ setting/ delivered by who eg assistant or therapist)

Orthotics: Change (details of type and timing) Casting: duration & timing/ Other..

Additional Therapy interventions for CONTROL group (eg PT/Orthotics /Casting/ other..)

Physiotherapy: (Details of frequency/ content/ dosage/ setting/ delivered by who eg assistant or therapist)

Orthotics: Change (details of type and timing) Casting: duration & timing/ Other..

OUTCOMES USED IN THE STUDY (PLEASE LIST) IDENTIFY AS PER ICF - BODY STRUCTURE AND FUNCTION/ ACTIVITY/ PARTICIPATION/ QOL/ OTHER

Primary outcomes in Study:

What was/were the primary outcome(s)

How was primary Outcome assessed

(questionnaire, observation, goniometer,3DGA etc)

Who completed the primary outcome measure

How were the primary outcomes obtained (face to face, telephone interview, postal other)

Place of outcome assessment (outpatients/home etc.)

Results of primary Outcome Measures

Mean scores on primary outcome at baseline (S.D)

Mean score at follow up (S.D) NB referring to Any Minimally important clinical difference (MCID) or Minimum Detectable Change (MDC) values note any statistical significance

Secondary outcome(s) in Study

List secondary outcome(s)

How was secondary Outcome assessed (questionnaire, observation, goniometer,3DGA etc)

Who completed the secondary outcome measure

How were the primary outcomes obtained (face to face, telephone interview, postal other)

Place of outcome assessment (outpatient/home etc.)

Results of secondary Outcome Measure(s)

Mean scores on secondary outcome measures at baseline (S.D)/ Mean score at follow up (S.D) NB referring to Any Minimally important clinical difference (MCID) or Minimum Detectable Change (MDC) values Note any statistical significance

Adverse events reported

Yes/No

(If Yes -Please detail)

PART 4: STUDY QUALITY

Quality if RCT:

1. How were the patients selected (convenience sample, all patients from data base, purposive sampling?)
2. Method of randomisation and allocation concealment (describe)
3. Method of blinding and who was blinded (describe)
4. Method of analysis (per protocol, intention to treat)
5. Study groups comparable at baseline (list factors on which groups were compared)
6. Number of participants lost to follow up (give numbers overall and for each group and reasons for attrition)

Quality if non randomised design:

1. On what factors were groups compared at baseline and were they comparable?
2. How were participants allocated to groups

Quality for ALL studies:

1. Were hypotheses stated prior to study
2. Were all aspects of the study conducted prospectively?
3. Was the intervention comprehensively described and replicable.
4. Were any adjunctive therapies comprehensively described and replicable?
5. Was training for the outcome measures described?
6. Were validated measures used for outcome measures
7. Were confounding factors considered? If so which?
8. What methods were used to control for any confounding
9. In comparative studies were participants seen within same time frame in each group?
10. Was the fate of all patients enrolled in the study adequately described?

Level of evidence I-V (American Academy of CP levels of evidence)

Any further comments about this study

14.9.5 Systematic Review- Levels of evidence and Conduct questions **AACPDM**

Levels of evidence used by AACPDM (modified from Sackett)

Level	Intervention (group) studies
I	Systematic review of randomized controlled trials (RCTs) Large RCT (with narrow confidence intervals) ($n > 100$)
II	Smaller RCTs (with wider confidence intervals) ($n < 100$) Systematic reviews of cohort studies 'Outcomes research' (very large ecological studies)
III	Cohort studies (must have concurrent control group) Systematic reviews of case-control studies
IV	Case series Cohort study without concurrent control group (e.g. with historical control group) Case-control study
V	Expert opinion Case study or report Bench research Expert opinion based on theory or physiological research Common sense/anecdotes

Conduct questions AACPDM Conduct Questions Group studies

Each question should be answered

"yes" =1 (criterion/criteria present) or

"no" =0 (criterion/criteria not present) or

? =0 for those studies unable to answer .

For group studies, the conduct of an individual study will be judged as Strong ('yes' score on 6-7 of the questions), Moderate (score 4 or 5) or Weak (score <4)

(Darrah et al., 2008)

14.9.6 Systematic Review – Table of methodology and results of included studies

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Bjornson et al. (2007)	Seattle, USA Single site Data collected between October 1997-September 2001 2 baseline assessments (7 days apart) and follow up 3,8,12 and 24 weeks post BoNT-A Study funded by Research grant NCMRR <i>Botax was provided by Allergan</i>	OnabotulinumtoxinA (Botox-Allergan) EMG guided injections into gastrocnemius muscle Dose: 12 units/kg (up to a max 400U) diluted at 100 U/ml Sedation: Midazolam sedation All children Toxin naïve Single injection cycle	Saline injections	Ongoing Physiotherapy (minimum 60-minute session per week) No directive regarding type quantity and casting or orthotics	56 AE reported over 24 weeks (30-BoNT-A group 26-placebo)	At 3 weeks Statistically significant decrease compared to placebo in QEK (p=.05), Achilles DTR (p=005) and clonus (p<.001) At 8 weeks Significant decrease in SMS total (p=.04) and elastic path length (p=.05) compared to placebo At 12 weeks Statistically significant increase in ankle dorsiflexion PROM with knee extended (p=.05) at 12 weeks (mean difference of 4.2°) Greater change in COPM-Performance score at 12 weeks (p=.04) for intervention group (1.7 points change) At 24 weeks > change in Vol torque at 24 weeks (p=.03) in favour of BoNT-A GMFM -88 and 66 scores consistently improved up to 24 weeks and were statistically significant in favour of BoNT-A at 24 weeks(p=.001 and p=.03 respectively) Improvement at 12 and 24 weeks but no significant difference in COPM-Satisfaction or GAS scores at any time point in favour of BoNT-A. (p>.12-.98) MAS no change at any time point	Although changes were observed in a number of outcomes in each ICF domain. The study failed to demonstrate a match between measured effect and perceived functional benefit. Although some significant physiological and mechanical effects noted at 6 months, family satisfaction with outcomes were unchanged. The authors conclude that there may not be enough functional change or family perception of functional change to register as meaningful improvement in their societal participation
Delgado et al., (2016)	Multi centre international trial. (23 centres, 6 countries) Data collected between July 2011-June 2014 Time points: baseline, 4 weeks & 12 weeks [+ discretionary visits week 16, 22 +/- 28 for patients not requiring reinjection] Study funded by Ipsen Pharma	Abobotulinumtoxin A (Dysport-Ipsen) EMG or ultrasound guided injections into gastrocnemius muscle (2 sites in upper quadrant and lower quadrant) and soleus (2 sites in lower quadrant) Max dose of 30 U/kg or 1000U diluted at 500 units in 2 ml saline. Two groups ABO ₁₀ U/kg/leg and ABO ₁₅ U/kg/leg Centres followed their usual sedation protocols 122 children were toxin naïve 113 had previous injections Single injection cycle	Placebo saline injections	An established physiotherapy and/or orthotic regimen was permitted provided that it had begun >1 month before study start and was maintained throughout the study (No details given regarding therapy content)	18 Treatment related adverse events were reported. Placebo n=7 and Total ABO n=11 (ABO ₁₀ U/kg/leg n=6, ABO ₁₅ U/kg/leg n=5) 144 children reported at least 1 Treatment emergent adverse events TEAE (not related to treatment) most were of mild intensity. In all groups, the most frequently reported TEAEs were upper respiratory tract infection.	GAS Both ABO groups showed better than expected goal achievement adjusted mean [SE] GAS score in comparison to the placebo group at 4 weeks post injection 51.5 [1.3] for ABO₁₀ U/kg/leg / 50.9 [1.3] for ABO₁₅ U/kg/leg Children in the placebo group did not reach the expected level score 46.2 [1.3]. The adjusted mean (95% CI) treatment differences were both statistically significant versus placebo 4.65 (1.59 to 7.71; p=.003) ABO₁₅ group and 5.32 (2.31 to 8.32; p<.001) ABO₁₀ group MAS muscle tone also significantly improved with ABO treatment (both doses) compared with placebo. The adjusted mean (95% CI) treatment difference versus placebo was -0.49 (-.075—0.23; p<.001) in ABO₁₅ group and maintained at 12 weeks And -0.38 (-0.64 to -0.13; p=.003) in ABO₁₀ group this was still significant at 12 weeks p=.04 PGA scores showed adjusted mean (95% CI) treatment difference versus placebo was 0.77 (0.45 to 1.10) for ABO₁₅ group and 0.82 (0.50 to 1.14) in ABO₁₀ group These were significant for both ABO groups versus placebo (p<.001). This significant difference continued at 12 weeks Tardieu showed angle of catch (XV3) at week 4 (treatment effect 7.4 (3.5 to 11.3) in the ABO₁₅ group (p<.001) but although positive change this was not significant in ABO₁₀ group	Single injections of both doses of abobotulinumtoxinA (10 and 15 U/kg for unilateral injections, 20 and 30 U/kg for bilateral injections) significantly reduce muscle hypertonia and spasticity translating into clinical and functional benefits

<p>Hastings-Ison et al. (2016)</p>	<p>Two sites (Royal Children's Hospital & Monash, Melbourne) Australia</p> <p>Data collected between December 2007-October 2012</p> <p>Funding: Australian National Health and Medical Research Council</p> <p>Assessment time points</p> <p>Baseline and approximately 26 months</p> <p>(3DGA performed at baseline and 4 weeks after final injection)</p>	<p>OnabotulinumtoxinA (Botox-Allergan)</p> <p>Into calf complex</p> <p>6 U/kg bodyweight with 12 monthly injections</p> <p>Dilution 100 U in 4 ml normal saline.</p> <p>EMG guidance under mask anaesthesia</p> <p>Two sites in medial belly one site in lateral belly of gastrocnemius</p> <p>Children with spastic diplegia had 6U/kg into each limb</p> <p>And hemiplegia had gastrocnemius and soleus injections of affected side</p> <p>Max total dose 18 U/kg (available for other muscle groups if indicated)</p> <p>Total mean dose per injection 183 U/kg (78U/kg)</p> <p>All children were toxin naive</p>	<p>OnabotulinumtoxinA (Botox- Allergan)</p> <p>Into calf complex</p> <p>As per intervention group but frequency was 4 monthly injections</p> <p>Total mean dose per injection 185 U/kg (79U/kg)</p> <p>All toxin naive</p>	<p>Usual care Physiotherapy</p> <p>Orthotic provision</p> <p>Matched funding for Physiotherapy post injection for both groups.</p> <p>2 children in 4 monthly injection group received serial casting</p>	<p>No serious adverse events reported, mild and moderate events similar between groups (43% 9 per injection episode in 12monthly group, 34% 7 in 4 monthly group).</p> <p>Children in 4 monthly group had twice the number of adverse events. Most common - flu like illness and falls. 2 children attended A+E on evening of BoNT-A - one with seizures due to omitting medication and one with post injection vomiting. Adverse events per child per yr. of treatment = 1.2 in 12 monthly group and 2.2 in 4 monthly group.</p>	<p>Both groups maintained passive ankle dorsiflexion and no significant difference from baseline to 26 months between 12 mthly and 4 monthly injection groups (3.3 degrees greater in 12 mthly group, 95% CI -4.7 to 11.2, p = 0.41). Difference in mean passive dorsiflexion change was 2 degrees (95% CI -5 to 9.1).</p> <p>Both groups demonstrated motor responsiveness to final injection on BoNT-A (increased dorsiflexion during stance), no significant between group differences (p=0.19), FMS 50m and FAQ additional activities score were slightly better in 4 monthly than 12 monthly group but not statistically significant. No significant differences for FMS 5m or 500m, functional activities with the FAQ or any domains of Child Health Questionnaire.</p> <p>Subgroup analysis revealed children with hemiplegia had less passive dorsiflexion than children with diplegia regardless of injection frequency (p=.001). A large effect size between two groups was shown (0.80). Children with Hemiplegia had a mean 8.5°(SD 14°) reduction in passive dorsiflexion (9° with 4 monthly and 8.1° with 12 monthly injections) over 26 months. Children with Diplegia had a mean increase of 1.6°(SD12°) passive dorsiflexion (0.1° with 12 monthly injections and 3.1° with 4 monthly injections) over 26 months.</p>	<p>No significant difference between 12-monthly and 4-monthly injection regimens on passive dorsiflexion or secondary outcome measures.</p> <p>Authors recommend 12 monthly injections</p> <p>Showed significant difference between hemiplegia and diplegia in subgroup analysis</p> <p>Children with hemiplegia lost range over 26 months and those with diplegia gained range</p> <p>Concerns re increasing crouch with increased dorsiflexion.</p> <p>Hamstrings injections in Diplegic patients may be a confounder</p> <p>No control group</p>
------------------------------------	---	---	--	---	---	---	---

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Kelly et al. (2019)	<p>Single site Canada</p> <p>Data collected between January 2008- December 2014</p> <p>Funding: Nova Scotia Health Research Foundation, Physiotherapy Foundation of Canada, IWK Health Centre Halifax, Nova Scotia</p> <p>Assessments at baseline, 1,2,6 months</p>	<p>OnabotulinumtoxinA (Botox- Allergan)</p> <p>BoNT-A+ 3 weeks casting using serial casts (weekly change)</p> <p>injections into gastrocnemius and soleus (+ hamstrings in 1 child)</p> <p>Mean dose 107.8 U (Range 100-150U)</p> <p>*Product not identified in paper, but Botox used (personal communication Kelly October 2021)</p> <p>No further details of administration or sedation</p> <p>7 children were toxin naïve</p> <p>Single injection cycle</p>	<p>OnabotulinumtoxinA (Botox- Allergan)</p> <p>BoNT-A+ Single cast for 3 weeks</p> <p>injections into gastrocnemius and soleus (+ hamstrings in 2 children)</p> <p>Mean dose 106.0 U (Range 100-140U)</p> <p>8 children were toxin naïve</p>	<p>Usual care PT during trial</p> <p>(No detail of content varied from none 30%, once every 1-2 months 20% to once every 4-6 months 50%- no difference between groups)</p>	No AE reported	<p>MTS showed significant effects of time for R1 (spasticity) and R2 (ROM) ($p < .001$) as did MAS but not group- by- time at each time point up to 2 months but this was no longer significant by 6 months</p> <p>No significant effects of time or group by time were found for spatiotemporal parameters of gait</p> <p>Significant effects of time were found at all time points for GMFM-66 ($p = .002$) and all PEDI domains except social function caregiver assistance ($p = .009$ to $p < .001$)</p> <p>Increasing scores over time in PEDI exceeded MCID in 4 out of 6 domains except for social function caregiver assistance and mobility caregiver assistance</p> <p>No significant change was seen in CPQOL</p>	<p>Study found no difference in magnitude of effects for two casting protocols. Authors suggest families may find one cast more convenient than 3 changes post BoNT-A.</p> <p>Function and participation continued to improve over 6 months and although BSF measures were no longer significant they had not returned to baseline.</p> <p>The magnitude of change in function and activity did not appear to result in change in QOL leading the authors to suggest CPQOL may not be sufficiently sensitive to change over time.</p>

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Lowing et al. (2017)	<p>Single site Sweden</p> <p>No funding details</p> <p>No details of data collection time frame</p> <p>Assessments at baseline, 3,12 24 months post injection</p>	<p>OnabotulinumtoxinA (Botox-Allergan)</p> <p>Ultrasound guided injections into plantarflexors +/- other leg muscles as required</p> <p>Sedation: Topical anaesthesia, paracetamol, and nitrous oxide</p> <p>Dose: 5.9 (1.7) U/kg body weight BoNT-A dilution 50 U/ml saline. Number of sites dependent on muscle mass. Variable number of injection episodes over 24 months (1-4)</p> <p>24 children were toxin naive</p>		<p>Usual care PT ranged from 2-4 times a month post injection for 3 months (included goal directed treatment focus). Each child had a home and school training programme supervised by PT</p>	<p>No AE reported</p>	<p>GDI increased by 4.1 points (95% CI 0.7:7.5. p=.02) after 12 m, ss; unclear clinical significance.</p> <p>GDI Categorical outcome at 24 months: Improved n=15; unchanged n=14; deteriorated n=7.</p> <p>Children with lower GDI before treatment had most increase at 3 months. No correlation between GDI and MAS, ROM, SMC at any time point.</p> <p>Median rating for spasticity lower at 3m 2 (1,2) (p<.001) no further changes at 12/24 months. PROM increased from baseline at 3 months (+6°, p<.001) and decreased again at 12m and 24 months (p=.01). SMC increased baseline to 24 m; GAS sig increase, 29/40 children attained or exceeded expected level. Median GAS T score 50 at 3 and 12m, 60 at 24. At 3 months GDI change scores correlated with GAS change scores; at 24 months GAS change scores correlated with SMC, but not MAS.</p>	<p>BoNT-A injections had a positive effect on spasticity reduction, but this was not related to improvement in Gait or Goal attainment.</p> <p>Improvement in Ankle ROM at 3 months was not maintained at 12 or 24 months. The influence on desired activities of daily living via goal attainment was significant and 80% of children attained or exceeded desired level of Goal attainment by 24 months. Clinically meaningful changes in gait did not occur during study but the authors argue neither did potential deterioration.</p>

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Schasfoort et al. (2018)	<p>Multi-centre study</p> <p>2 University hospitals and 5 Rehabilitation centres Rotterdam, The Netherlands</p> <p>Recruited between October 2009-September 2017</p> <p>Funding: Netherlands Organisation for Research and Development and Rijndam Rehabilitation, Rotterdam, The Netherlands</p> <p>Assessments at baseline, 12 weeks (when CR ended) and 24 weeks</p>	<p>OnabotulinumtoxinA injections (Botox- Allergan Inc., Eindhoven, The Netherlands) + Comprehensive rehabilitation</p> <p>Injections administered under general anaesthesia by experienced clinicians in a paediatric hospital day-care setting. Clinicians adhered to recommendations, as described in the European Consensus 2009 (5) and age- and weight-related maximum allowed doses were injected.</p> <p>Mean dose 9 U/kg (5)</p> <p>Variety of muscles as clinically indicated (10 +listed)</p> <p>8 children toxin naïve</p> <p>34 had previous injections</p> <p>Single injection cycle</p>	<p>Comprehensive Rehabilitation</p> <p>15 children toxin naïve</p> <p>9 children had previous injections</p>	<p>12 weeks of Comprehensive Rehabilitation: Individually tailored high intensity goal directed Physiotherapy (IPT) +/- serial casting + AFOs. Detail regarding IPT guideline provided and therapists IPT diaries</p>	<p>No AE Reported for either group</p>	<p>Pain - no significant difference between groups</p> <p>AoC (dynamic tone) of the rectus femoris muscle was a clinically relevant difference in effect in favour of the only-CR group (12° difference between groups, $p = 0.025$).</p> <p>Kinematic gait parameter maximum knee angle during the swing phase while walking barefoot was the only effect outcome that showed a statistically significant and clinically relevant difference in effect in favour of the BoNT-A+CR group (6° difference between groups in favour of BoNTA+)</p> <p>CR, $p = 0.034$.</p> <p>GAS showed similar patterns of improvement for both intervention groups at 3 and 6 months (NS $p=.791$ and $.688$) casting periods and/or alignment of AFOs was complicated in both groups, mainly due to pain and pressure complaints.</p> <p>No adjustments made for multiple comparisons and counted muscles injected (with an additional left right adjustment)</p>	<p>Showed an improvement of GMF in both groups .</p> <p>At the group level giving BoNT-A prior to rehabilitation did not increase the effectiveness of multimodal CR treatment for ambulatory children in this study. Outcomes were measured throughout ICF therefore need to consider the indications for use of BoNT-A in this group.</p> <p>Due to disturbed randomisation the authors warn against attributing statistical significance to clinical significance due to disturbed randomisation</p> <p>No control group of usual care of therapy</p>

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Thomas et al. (2016)	<p>Single site, Queensland CP Health Service, Australia</p> <p>Funding; Queensland Health Community Rehabilitation Research Scheme & Royal Children's Hospital Foundation Grants</p> <p>Assessments: baseline, 10-12 weeks & 26 weeks</p>	<p>OnabotulinumtoxinA (Botox-Allergan PLC)</p> <p>To one or more lower limb muscles as per published 'We Move' guidelines (no details of specific leg muscles injected)</p> <p>BoNT-A + Group therapy</p> <p>No information about previous injection history</p> <p>Single injection cycle</p>	BoNT-A + Individual therapy	<p>All children received 6 hours Physiotherapy six x 60 mins sessions IND 1:1 PT and GRP had 1 PT:4/6 children (+ assistant or PT student) so 1:3</p> <p>Both groups had HEP casting and orthotics as required</p>	No AE toxin related one casting AE	<p>COPM - SATISFACTION no difference between intervention groups immediately post intervention; at 26wks ss difference for GRP (not clinically meaningful).</p> <p>PERFORMANCE no difference between intervention groups. GRP made ss and clinical meaningful differences at 10 and 26 weeks in both perf and satisfaction; IND ss at 10 and 26 weeks, clinical meaningful at 10 weeks not 26</p> <p>EVGS no ss difference b/w or within groups</p> <p>CP-QOL access to services significantly different for GRP at 10 weeks</p> <p>No sig differences between groups on any other measures. PRT within group gain IND at 10 weeks, retained at 26 weeks. GMFM no in group improvements either group (no statistical analysis reported) 1MFWT GPR showed significant difference from baseline</p>	Both groups demonstrated clinically significant improvements in COPM P and

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Valentine et al. (2020)	<p>Single site, Perth Australia</p> <p>Funding: The GMFM assessment time was funded by an unrestricted post graduate education grant from Allergan. Allergan had no role in the design of the study, collection, analysis, or interpretation of data or writing of the manuscript.</p> <p>Data collection period (not specific)</p> <p>GMFM-66 Assessment at T2 only</p>	<p>OnabotulinumtoxinA (Botox-Allergan) N=27</p> <p>No details of administration</p> <p>Median (IQR) Total dose per treatment= 6.95 U/kg(4.4,11)</p> <p>Median (IQR) dose per muscle= 2.95 (2.2,4) U/kg/muscle</p> <p>Mixed lower limb injections (multilevel)</p> <p>Proximal, distal)</p> <p>Multiple injection cycles</p> <p>(Median 11 (6.71,5.5)</p>	N/A	<p>Usual care provided by community provider</p> <p>Extra therapy provided following toxin (8 extra sessions per limb injected)</p>	Not reported	<p>Results described in terms of changed GMFCS level</p> <p>6 (21.4%) Improved to GMFCS Level I . Mean GMFM-66 score 86.9% (5 Hemiplegia,1 diplegia)</p> <p>22 children remained GMFCS II (78.6%) GMFM-66 mean score 72.6%</p> <p>Pain (scored from 26 children) 10 children (38.5%) complained of pain Mean score 3 (SD 2.4). No relationship with pain and comorbidities or BMI</p> <p>Median Participation frequency was 6.1 (5.4,6.5) in Home, School 3.6 (3.4,4.6) and community 2.2 (1.6,3.0)</p> <p>No statistically significant relationship between PEM-CY score and topography, final GMFCS level or Pain. Only statistically significant negative association between school participation and GMFM centile correlation coefficient of -0.5 (p=.01)</p>	<p>The authors claim that this study confirms that the majority of highly treated population remains at a stable GMFCS level and the GMFM-66 average is consistent with published average levels (where patients who had undergone treatment with BoNT-a , SDR ,ITB were excluded). For a small number the GMFCS level had improved and none had declined</p> <p>The study confirmed that children with CP at GMFCS level II treated at a young age with repeated low to moderate doses of BoNT -A within an integrated comprehensive service maintain their functional motor gains at a later age</p>

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Williams et al (2012)	<p>Single site, Perth Australia</p> <p>Funded by Princess Margaret Hospital(PMH) Foundation grant and University of Western Australia's (UWA) Research and Development Award.</p> <p>Assessments baseline x2 12 weeks and 2 weeks before injections, approximately 5(1) weeks post injection and 14 weeks post injection</p>	<p>OnabotulinumtoxinA (Botox-Allergan)</p> <p>All children had bilateral Gastrocnemius injections 2-6 U/kg (+/- muscles as clinically indicated no child had more than 3 muscles injected per leg)</p> <p>No administration details</p> <p>GMFCS details not given</p> <p>Previous injection history : minimum of 2 previous injection cycles (mean series=8.93, maximum series=15)</p> <p>Children randomised to pre BoNT-A or Post BoNT-A strength training</p>	<p>8 of the 15 children also completed a 6-month pre - intervention baseline phase = control period.</p> <p>Mean age 8 .2 years (SD 2 years), (n = 6 GMFCS I, n = 2 GMFCS II), took part in a control phase prior to continuing onto the intervention phase.</p>	<p>Home based strength training programme 3 times a week for 10 weeks (programme progression fortnightly by exercise physiologist using American College of sports medicine guidelines, family member trained delivered programme) + usual PT</p>	<p>No adverse events reported</p>	<p>Spasticity was significantly reduced post injection in summed MAS scores reduced at 6 weeks (p=0.033). No significant change in MAS with either strengthening programme (p>0.05)</p> <p>Motor control, SCALE scores whole sample increased at 6 months from baseline to final assessment[t(13)=-2.686,p=.019,ES=.56]</p> <p>Children made significant isokinetic strength gains (mean p=.022, ES 0.57) in the intervention period in comparison to the control period (mean p=0.15, ES 0.56)</p> <p>Irrespective of timing significant strength improvements were seen at 10 weeks and 6 months.</p> <p>Functional improvements were shown in Gas immediately (p=.007,ES 4.17) and at 6 months(p=.029, ES 0.99).</p> <p>Improvements in MV were seen in all assessed muscles both over control and strengthening phase apart from dorsiflexors which only showed over strengthening period(p<.001,ES=.80). Changes over control and strengthening intervention not statistically significantly different.</p> <p>Both pre and post toxin strengthening showed an improvement in strength at 6 months with no significant difference</p>	<p>Home based strength training based on individual goals was shown to improve strength and functional goal attainment. Both pre and post BoNT-A strengthening programmes showed an improvement. The authors suggest that Pre training may be more suitable for those children requiring casting post injection. They recommend targeted strengthening programmes including the injected muscles.</p> <p>Suggested improvement of BoNTA + strengthening is superior to BoNT-A alone.</p>

Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Wright et al. (2008)	<p>Single site, Toronto Canada</p> <p>Funding Bloor view Children's Hospital Foundation</p> <p>Assessments at baseline 2 months and 6 months post injection</p>	<p>OnabotulinumtoxinA (Botox-Allergan)</p> <p>mean BoNT-A dose was 11.5U/kg (SD 5.9) with a mean total dose of 207 units (SD 82.9)</p> <p>No further administration details Variety of muscles injected</p> <p>Gastrocnemius</p> <p>Muscle injected=29children</p> <p>(Alone or in combination with other muscles)</p> <p>Hamstrings muscle= 21 children (alone or in combination)</p> <p>Hip adductors=7 children (alone or in combination)</p> <p>17 children were toxin naive</p>	N/A	No details given	Not reported	<p>Reduction in dynamic spasticity (R1) at 2 months in gastrocnemius and hamstrings (p<.05). Improvement was maintained at 6 months in injected gastrocnemius muscles (p<.001)but no longer significant in hamstrings.</p> <p>Improvement in timed walk maintained over 6 months (p<.05). Improvement at 2months in GMFM D& E (p<.01) and further improved over 6 months(p<.001). For activity and participation measures there were changes of at least 3.0 points (maximum p<0.001) by 6 months for all subscales except the PODCI upper extremity.</p> <p>Activity and participation measure changes generally were most notable from baseline to 2 months with either maintenance of gains or continued improvement through to 6 months.</p> <p>Despite this change score relationships between measures of body structure and function (spasticity and timed walk), activity (GMFM & PEDI) and participation (PODCI) at 2 months and 6 months were poor to fair (r<.40). Predictor combinations accounted for <69% of variation in activity and participation scores. Predictors often pertained to baseline score, GMFCS level or age.</p>	<p>Improvements were demonstrated following BoNT-A injections in all ICF measures.</p> <p>Despite moderate to strong pairwise relationships for many of the BSF and activity & participation measures at baseline, the strength of change score relationships was typically no more than fair. Similarly activity and participation baseline relationships were strong this was not evident in the corresponding change score relationships.</p> <p>Notably spasticity variables accounted for less than 50 % of explained variation in GMFN,PODCI and PEDI change score models.</p> <p>The relationship between changes at different ICF levels were complex and authors suggest multi factorial.</p>

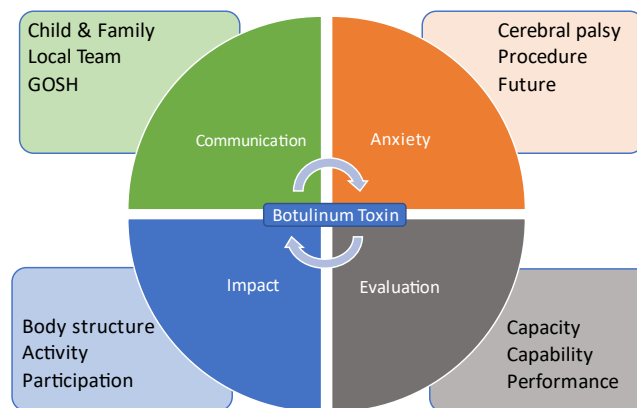
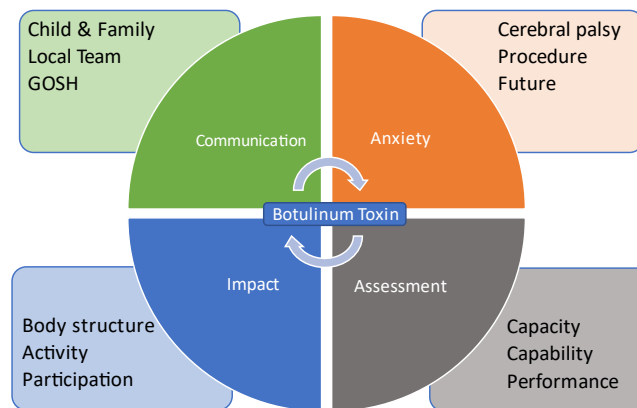
Study	Characteristics of Study <i>Country/Funding/ number of sites data collection points</i>	Characteristics of BoNT -A Intervention <i>Including previous BoNT-A history, number of cycles)</i>	Comparison group	Adjunctive measures	Adverse events (AE)	Results showing a relationship between change in BSF and ICF Domains	Study conclusion
Yap et al. (2010)	<p>Single site, Shriners hospital for children, Montreal, Canada</p> <p>Funding: Shriners hospital, Montreal Children's hospital research unit and L'ordre professionnel de la physiotherapie du Quebec</p> <p>Assessments at baseline and 3 months post injection</p>	<p>Botox (Markham,ON,CA)</p> <p>8-15 U/kg.</p> <p>Mean dose 9.1 U/kg (SD 1.9) Mean total dose injected 186.1 U (SD 85.2) Conscious sedation used injections into gastrocnemius</p> <p>2 children had additional upper limb injections</p> <p>9 children were toxin naive</p> <p>15 had previous injection episodes (range 2-7 episodes)</p>	N/A	<p>Below knee walking cast 1 week post injection. Cast changed every 1-2 weeks until passive ankle dorsiflexion of 10-15 degrees achieved (mean 20.6 days SD 8.9). Then AFO worn for half day +/- all night. PT commenced after cast removed, one session every 1-2 weeks. Details given of generalised therapy content</p>	NoAE reported	<p>BoNT-A injections + casting showed statistically significant change in all outcome measures.</p> <p>Statistically significant change from baseline in PROM and AROM, mPRS and MAS (p<.001), GMFM-66 and FAQ (p=.005).</p> <p>No significant change in functional independence (WeeFIM)</p> <p>No significant correlation between any of the individual exposure variables (age, number of treatments distribution or severity of CP, parental stress, or child's motivation) and change in muscle tone</p> <p>multivariable analysis there was an association with low social persistence and low levels of parental stress with greater change in tone (p=.006-.017). Significant correlation (r=.39-.41) between child's motivation and change in gait pattern</p> <p>Younger age (p=0.015) and fewer number (p=0.024) of BoNT-A treatments were associated with greater change in gross motor function. Child's motivation and parenting stress were significantly associated with improvements in muscle tone (p=0.006-0.017), passive range of motion (p=0.008-0.033), gait pattern (p=0.005-0.042), level of ambulation (p=0.001-0.043), and functional independence (p=0.004-0.027).</p>	<p>First paper to Looked at parental stress and child's motivation on responsiveness to toxin treatment and the modifying effect of these variables on muscle tone PROM gait pattern level of ambulation , gross motor function and functional independence.</p> <p>BoNT-A injections + casting showed statistically significant change in all outcome measures. However, younger age and fewer number of BoNT-A treatment were associated with greater change in gross motor function. Child's motivation and parenting stress were also significantly associated with improvements in muscle tone, PROM, gait pattern, level of ambulation and functional independence</p> <p>Preliminary study exploring interaction between modifying factors looking at factors that may predict level of responsiveness Studies focus on age cp type severity ambulatory status BUT clinicians acknowledge effect of motivation and family coping on developmental outcomes but not measured in a clinical setting.</p> <p>The results suggest age number of treatments parental stress and child's motivation can influence the degree of responsiveness . The findings suggest that the contribution of contextual factors(personal environmental) in influencing outcomes is under appreciated in this population.</p> <p>Child motivation and parental stress are potentially modifiable.</p>

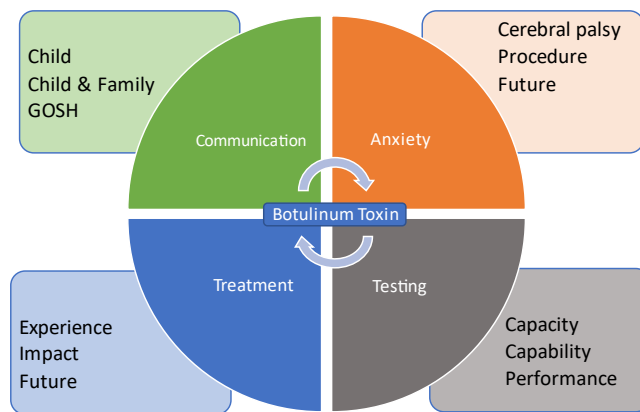
14.10 Thematic analysis

These are the initial themes established from initial coding of the transcripts including additional notes by the researcher. These initial themes were developed and reviewed as potential themes then re-visited on a number of occasions and refined and further defined and named as in Chapter 11 in order to answer the research question

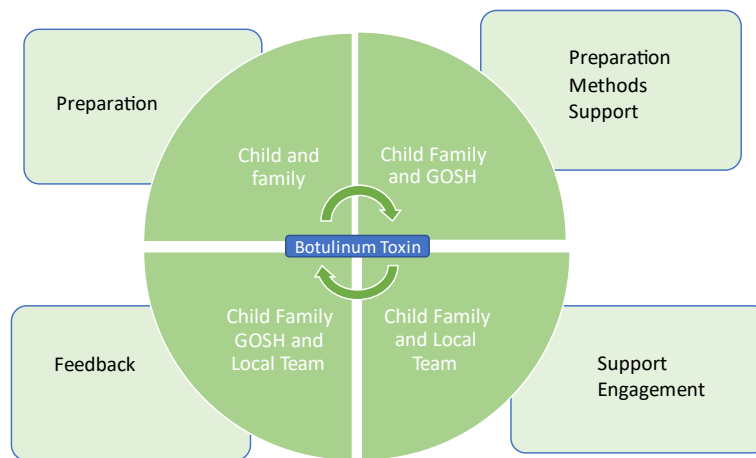
'Are standardised assessments and current procedures picking up what is important to children and their families following BoNT-A?'

Themes initial mapping





Communication Theme mapping



GOSH and family (C_G&F)

General Feedback on communication /experience

You do (*support*) because on certain events like obviously when we came post Botox there would be some things I've noticed that M will be struggling with, and a few of your colleagues or even yourself I believe have printed off, ..local clubs in the area that M could benefit from. ... like a CP football group which was fantastic that

you guys printed off. SNAP, you guys were the ones that told me about SNAP, which was really good. ...[SIGNPOSTING *how GOSH offers practical post injection support* PARTICIPATION -[1,F,5,1,M_G] *positive for service delivery*]

Just the feedback for this place, I think it's amazing because, you know, there's lots of time for questions and there's really good assessment.... I think if anything, it is a little bit difficult to get hold of doctor outside of the appointment. 33,M,4,III,M_G]

Preparation (C_G&F_prep)

All of it, fantastic. More than enough information. The whole procedure itself, the care, ..., I mean, this isn't just one person, there's like a team of five the whole time, whether they're the play or they're the physio or you or anyone, I mean, surrounded by professional care. I feel it was a perfect experience. [66,F,4,III,M_P
Team around the child

I was more than happy with the preparation going into the injections, not an issue. I think, on the day, again it's a difficult day, so it's hard to assess. [70,F,4,III,P_M]

We were aware that there was going to be a bit more wobbliness but we would still make her do the same things prior to the botox, and then just assisted her a bit more, than slowly ease off. So, I think we were quite positive in that respect. Because you have to know things, like the toilet. Yes, it's very, very important. [70,F,4,III,P_M] *prep for the injections and knowledge of side effects*

Pre clinic and preassessment preparation Yes, and I think it's good. Because, you know, you talk to the adults as well, but children are also involved in it, so you don't hide anything from them. Now .. had it done, I definitely wouldn't say it's anything to be worried about. [59,M,6,III,M_P]

No, to be honest, the information, it meant, as parent, it meant everything was perfect Yes, because everything was explained, if we had any questions, we felt we could ask them, and no question was too stupid..Oh yes, and it's nice that you

ring the day or two before just to remind us, it's good, with everything else that goes on and all the other appointments that you get with a disabled child, sometimes you do forget...[10,F,4,II,M_P]

No, to be honest, the information, it meant, as parent, it meant everything was perfect. REPEAT QUOTE [10,F,4,II,M_P].

communication with the team) Yes, fantastic. Yes, amazing. I knew what was going to happen, your whole team spoke to me, told me what to expect and where would go from here, so I was fully aware. [7,M,12,1,M_G]. *Impact for service pre assessment appointment is important first time*

you already send us a letter, we come in when it says, we've never had any issues- ...,We get sufficient notice that I can rearrange my work schedule to, sort of, work from home. [62,F,10,I,M_G]

Different communication methods- suggestions (C_G&F_sugg)

Not really. I think maybe-, I don't even know if this is possible, but for example when he had his tonsils out, they had like a little book they'd made. Like a little booklet. And it detailed everything. They gave it to us at the pre-assessment. On the lead up to him having his tonsils out, every day they'd get this book out at some point and explain what was going to happen. Maybe something like that for the first time. [59,M,6,III,M_P] *information via a booklet*

Yes, so for the first time they can see that they have to come-, I know they have in the playroom, (*play therapist has a prep booklet on the day*) well, in there, but maybe if you have little handouts for children to look at in the run-up-. And then, you know, the parents can just have a look at it so they can see that, actually, on the day, by remembering on the book it said you can have the cream on, and then they remember. Because I know on the run-up to the-, he kept asking me questions and he was getting himself in a state. And I was trying to reassure him, but kids

work with things a lot better when it's visual, [59,M,6,III,M_P] *preparation of child at home by parents, trying to minimise anxiety for the child*

Yes. I don't understand any of it though, that's the thing. When the reports come through, I don't understand....*could* Make it simpler. There are too many big words in it, and you-, I have to look it up. No, I bring it up to see what it says. What you're meaning by it.[3FM1_M] *medical jargon method of communication who are the reports for ?*

Everybody's so busy [1,F,5,1,M]....(?staff& parents)..If you just ask me via e-mail I think then it would take me five minutes, or X and I could have a quick chat rather than saving it for six months. [1,F,5,1,M_G](so I would) come to these meetings a bit more prepared [1,F,5,1,M_G] *feedback about injections keeping in touch between appointments (initial plan was to text monthly but thought too burdensome for families and researchers with numbers involved)*

If you say what the things that you want to see are, and then if we video it at different times, because we observe..... So, yes, there's a lot that you don't see. ...[16,F,4,I,M_G] *capacity vs capability and performance more realistic when see in home setting changed post covid with telemedicine should be easier to use and? upload to my gosh*

Parental Involvement around injection assessments ..

It's hard to remember between May and now. *..so would be good if team say We're going to see you in three months, just take some notes*[1,F,5,1,M] **Recall**

If you just ask me *via* e-mail I think then it would take me five minutes, or X and I could have a quick chat rather than saving it for six months. [1,F,5,1,M_G]

It would be good to ask the family for a quick assessment. [1,F,5,1,M]

If you say what the things that you want to see are, and then if we video it at different times, because we observe..... So, yes, there's a lot that you don't see.

...[16,F,4,I,M_G] *capacity vs capability and performance more realistic when see in home setting changed post covid with telemedicine should be easier to use and? upload to my gosh*

Communication outside GOSH_Others (C_OG)

GOSH and Local team / Family and Local Team

(*your*) communicating with my local team perfect, my local team communicating with you is the issue. ...[10,F,4,II,M_P]

After not expecting it to work and then it working really well, and that's what we-, because from our consultant's point of view, "we saw her after eighteen months and now we're not going to see her for another year"-,...[16,F,4,I,M_G] *Family not happy with lack of contact with local team even though they went through treatment with their child LACK OF A PLAN*

Anxiety : Parental +/- Child anxiety

Preparation of child /family (COMMUNICATION) (A_Prep)

So, that would've been helpful to have, maybe if you just say, 'This is what the experiences of other people are.' That really helps you, as a parent, to plan and to know, because the school also, they didn't know anything. They were like, 'Oh, she's going to have this done. We don't know what that's going to be at all.'It's how the adults around you behave, really effects if it's a big deal, making it a big deal or not. So, as it turned out, it didn't have an immediate affect and so it happened over a gradual period of time, and that was really good....[16,F,4,I,M_G]

if you have little handouts for children to look at in the run-up-,. And then, you know, the parents can just have a look at it so they can see that, actually, on the day, by remembering on the book it said you can have the cream on, and then they remember. Because I know on the run-up to the-, he kept asking me questions and

he was getting himself in a state. And I was trying to reassure him, but kids work with things a lot better when it's visual. [59,M,6,III,M_P]

because you've seen so many cases and you've seen the different things, that's so helpful for a parent because we are only experiencing it with this child, so we really don't know. -,....[16,F,4,I,M_G] *parents wanting advice from staff about different outcomes and experiences patients have experienced*

Procedure (A_Pro)

What we have learnt from this though, with X is because obviously the last time she had it, she decided to *fight* the anaesthetic *it didnt* work not until she'd actually had the procedure, which kept her asleep for hours. *Worried about next time*
[66,F,4,III,M_P]

I was more than happy with the preparation going into the injections, not an issue. I think, on the day, again it's a difficult day, so it's hard to assess. [70,F,4,III,P_M]

So, we didn't know what to expect, and we expected-, he kind of said that it might be an overdose the first time because you 'don't know how much you're giving', but you are cautious. I felt like there wasn't that much information, actually, about that process at all. I think that's probably because each case is different. So, that's what they ...transparency about everything just makes it more-, and that why I don't mind you talking to her about it because actually, we're being very pragmatic about everything and that's worked really well. ...Each case is different, but it means that you're not prepared as a parent for what will happen [16, F,4, I,M_G]

Yes, I was a bit anxious. But more *for* him than me, because obviously he wasn't very aware of what was going to happen so it was me as a parent who was more scared and worried for him. But I felt so at ease. [7,M,12,1,M_G].

Well, they said it has an amnesic, which I hope it did. So, she just had a good time and she says that.. she can't quite piece it together, and we think that's good. [16, F,4, I,M_G]

Botulinum Toxin fears 'poison' (A_Btx)

Were you worried about it at all? Yes, I was a bit, because it's-, I didn't really understand what Botox is, you know. It's a toxin which doesn't sound very good does it? So, it is a bit worrying as a parent, I was quite worried on that aspect.
.[63,F,5,II,M_M]

And did you find out much information before? Yes, I was given a couple of leaflets to read and stuff. That sort of helped ease my mind a bit and I felt because that was what we've been recommended, so obviously, it can't be all bad, if they do that.[63,F,5,II,M_M]

I wanted it done before school so that when she went into school, she didn't feel as restricted, which seems to have worked [exp_timing].: But you don't know what the side effects are.... and back then, we didn't know. Because they said something about they can lose control of their bladder, but ..she was fine...there were no adverse effects. [70,F,4,III,P_M]

It's a shame there is no long term scale of how it [botox] affects you later on life, that's the only, that is the downside, but when you've got a child with cerebral palsy that you are so desperate for that child to run around with her peers and have a full life, because children don't stop, they will run and expect you to run with you and if you can't keep up, which she couldn't do, she would just sit in a corner with her head dropped. So for me the participation outweighs everything. [66,F,4,III,M_P]
it's never an easy decision to put your child to have more injections in their leg and all of that, but there's no downside and I think that's the important thing. We've seen no, nothing that's negative from the Botox. If anything, even though it is short-lived, that confidence takes her through many months. [66,F,4,III,M_P] (T_Confid)
(A_Btx)

we didn't know what to expect, and we didn't know if the day after she had it, she'd be in a lot of pain from deep muscle injections, or if she'd go all wobbly and that would have a quick effect because you'd have to go wobbly and then it would be

different. Then she has to relearn how to walk. So, we really didn't know what to expect -,....[16,F,4,I,M_G]

Post injection – at home /community (A_postBtx_home) A around effects of toxin

We were aware that there was going to be a bit more wobbliness but we would still make her do the same things prior to the botox, and then just assisted her a bit more, than slowly ease off. So, I think we were quite positive in that respect.

Because you have to know things, like the toilet (*warned of possible continence issues*) . Yes, it's very, very important.[70,F,4,III,P_M]

Managing expectations (A_manexp)

If you said look, you know, it could kick in at 24 hours, or it could take up to four to six weeks. It would pick up and really you don't notice it, or you might notice it straight away. It's a gentle thing, you know, that's the other thing. It's not this sudden thing where everything goes floppy. I thought she wouldn't be able to walk because this muscle would be floppy and that she'd have to re-organise. It's quite a gentle thing when it kicks in. That would have been really helpful to know.

....[16,F,4,I,M_G] *need to prepare parents for very small gradual effects in the majority of cases*

it's actually the physical operation that always worries me more than the actual giving of the injection[66,F,4,III,M_P] *less stress about inj vs ortho surgery*

So, I think that the consultant .. said that, you know, because she's mild, the changes and what will happen to her are almost too mild to be treated onto the NHS. She was just like, you know.... She just said it. I wasn't pressuring her or anything. I was just like, what's the plan or whatever? But that's what she ended up saying. You know, I know the next child came in with a big frame. So, I know that's just what they're, sort of, focussing on. She did actually say that. But the thing is, it (botox) made such a difference for her.16, F,4, I,M_G]..*concerns that*

children as 'mild' wont get treated.. feeling guilty that other children are worse off but you still want whats best for your child to realise their potential

Look, he's got, obviously, he's got a way to go, but it's not that, it's, like, trying to get the best out of him, the best that he can be [*Reach his potential*]. The best he can be, yes, and I think he's doing amazing, I mean, we're pleased with his progress... **And he feels very pleased**... he does, definitely! [33,M,4,III,M_G]

Further injections (A_Rpt)

I was more than happy with the preparation going into the injections [*first time*], not an issue. I think, on the day, again it's a difficult day, so it's hard to assess.....*but* She's not going to be the same this time. [*Mum expresses concern for next time*] [70,F,4,III,P_M]

I think that, again, looking back, my answer changed, so it's, sort of, role reversal because knowing that we're going back into that situation, it's different to not knowing. Not knowing, you're just trying to get through the day and prepare the best you can. But knowing that we're coming back to do that, there's a lot of factors there that need to be taken into consideration for it to be successful again. [70,F,4,III,P_M] [*father expresses concern for next time*]

Now I know that when we come back, for instance, we're going to use the localised cream, we're not going to use the sedative, you know, all sedative. That's never going to happen, it's never going to happen. She's aware of it now. So, I'm sitting here now going, 'Unless there's an improved game plan, we're really going to have a problem,' because she's going to come into that-, [*Do you think she's very anxious about it all now having had it?*] *mum*: She's been talking nothing but this set all day. She wasn't coming today because she didn't want the injections. [70,F,4,III,P_M]

'How do I, for lack of a better word, incentivise her coming?' because I really do think she's going to struggle to the extent of, 'I'm not doing it'. [70,F,4,III,P_M]

Uncertainty about repeated injections (A_Rpt)

So, it's now about seeing if we can jump up to a different level or if it's maintenance. If it's maintenance, then I'm not sure that's the way we need to be, but if we can hopefully just get even a 2% increase, then we're going the right way, aren't we? [70,F,4,III,P_M] *child was very upset during last procedure*

Parenting a child with CP (A_Par)

how they fit in at school and whether they're able to-, can they keep up in P.E. .
[1,F,5,1,M_G] *expressing concerns about what CP means for their child*

Emotionally it's that you really don't want them to feel left out in any way, so I think that is, I think, for reassurance for the parents really, really important. .
[1,F,5,1,M_G]

And I think, if she wants to do it, she will do it. Even if she'll have trouble, it doesn't bother her, she will get on [63,F,5,II,M_M] (also in Participation)

Emotionally it's that you really don't want them to feel left out in any way
[1,F,5,1,M_G]

This is the age now where he's starting to notice. Like, before, it never really bothered him, but he's now, he's noticed that there are things that his friends do that he can't do and he does get very angry, very frustrated. [51,M,5,II,M_G]

as he's getting older, he's noticing the difference a bit more so it is getting a bit harder but, yes, because he's a bit behind I suppose. But, yes, he still tries to join in and tries to keep up. [19,M,6,M_M]

Yes, I'm upset. I've put a lot into..... you know, he can walk, so I'm grateful for that, and he's really determined as well. Like, he hasn't really been using his frame in school because he doesn't want to be different, he says. He does fall over and stuff. He hasn't got very good balance, but it does make me sad to see the way he's walking because it's worse now when it shouldn't be really.It is affecting him quite a lot. He feels left out. [59,M,6,III,M_P]

I don't know whether it's because her cerebral palsy's getting worse or just because of winter. We're still learning how her body works in that-, but it's a drastic different in the cold. [60,F,6,II,M_P]

He's really struggling, especially lately. He's been getting upset because he wants to be the same as his friends in school. He falls over a lot. Finds it hard to do certain activities like soft play and things like that. Getting himself dressed, running, and he does get quite upset about it. And when it's really cold, it causes him pain as well. [59,M,6,III,M_P]

Parenting a child with CP_Preparedness (A_Par_Prep)

I also, I often wonder, and we talk about it a lot-, because at the beginning we spotted that something was a bit off. We amongst us as parents, we had some differences on whether we saw it or not and whether we thought something needed to be done about it. I can only imagine-, because it's not like, 'It's so obvious,' you know? So, I think the cases like her, I can so see how that would just slip through totally, and I wonder at what point that would have been (...*picked up*)..You know? Who would have-, I do wonder about that for other children, I think. [1,F,5,1,M_G] *Difference between parents opinion / mild CP so could be easily missed? Could this influence how parents feed back in an appointment :*

Do you know, like, when we first found out (*about CP*), I used to think, 'How will physiotherapy actually recover this? It's medicine that usually recovers, or operations that recover,' but I seriously believe in physiotherapy, like, it's amazing, you retrain the brain. I find it astonishing, to be fair. [33,M,4,III,M_G]

No, I don't think you'd know as a parent. I mean, of all the stuff you read up on and look out for, that would not be one that you would know, [1,F,5,1,M_G] ... *lack of support lack of information regarding CP*

So, I think that the consultant .. said that, you know, because she's mild, the changes and what will happen to her are almost too mild to be treated onto the

NHS. She was just like, you know.... She just said it. I wasn't pressuring her or anything. I was just like, what's the plan or whatever? But that's what she ended up saying. You know, I know the next child came in with a big frame. So, I know that's just what they're, sort of, focussing on. She did actually say that. But the thing is, it (botox) made such a difference for her.**16, F,4, I,M_G]***..concerns that children so mild wont get treated.. feeling guilty that other children are worse off but you still want whats best for your child to realise their potential*

Standardised Testing

Tests in clinic (Test_capacity)

Capacity vs Capability and Performance (How useful to measure)

If you say what the things that you want to see are, and then if we video it at different times, because we observe...., So, yes, there's a lot that you don't see. So, even though you spend ages doing a really good assessment, but you didn't see the things-, They've been trained (*children with CP doing repeated tests*), and that's really amazing that they do that, but it means that the result isn't the real-world result...**[16,F,4,I,M_G] [CAPACITY vs CAPABILITY & PERFORMANCE](Test_capacity)**

So, because what's harder is the practical, the sensory thing that's going on with her as well. So, it's almost like after a while of doing the exercises, it's almost like she's trained to do those exercises really, really well. (**CAPACITY / CAPABILITY**) That's what we've found, and she's particularly all very well in her last post-Botox assessment. Yesterday she saw her consultant, and again, if it's the same task, just walking that short distance, she can do it very, very beautifully, but as the doctor saw, walking into the clinic and walking out on the street, she kept putting this foot in front of that foot. It was going at an angle and she was stumbling over it. (**PERFORMANCE**) So, partly that's to do with when they give them more than one task to do at a time (*asking children to count etc to distract them*), which is what it's like in reality, but it's also just that, in a way, I think that they become very good at doing the same task. ...**[16,F,4,I,M_G] LEARNED CAPACITY REPEATED TESTING**

He loves it, he thoroughly enjoys it. He thinks this is the fun appointment, the more ones he goes to, he enjoys all the challenges because it's just him. He isn't really competing with anyone else, so it's all well. ...: If you were to mix it up and do, like, group sessions, you wouldn't get half of what you get. But because it's just him, and he doesn't feel he's got to. .. Because he feels, like, someone else is doing it better and *he* won't try so much.

[51,M,5,II,M_G]

She found them all quite easy. But hers, it's more the long-distance thing that would hurt her, or -, but then I don't know in a room, can you push her? I don't know. [63,F,5,II,M_M] [*realistic activities? & bikes? & endurance comments from parents*]

There's nothing intrusive. For me this is just her normal day in a more structured setting. So there's nothing intrusive. I mean this is just like a normal day and although she might be shy to do these exercises, this is common place for her[66,F,4,III,M_P.

Well, she goes through the whole list anyway.....She's told him today that it's too easy for her... It's too easy today! [3,F,1,M_M][*mum said child likes the tests*]

So, most of the assessments that you do are kind of like those physical tests. So, those are good. It's good that we could see the balance, the difference in the balance in each side, so that we can see what the next things are we need to work on. ...[16,F,4,I,M_G]

They've been trained (*child with CP*), and that's really amazing that they do that, but it means that the result isn't the real-world result. So, that has definitely happened in this time. ...[*disconnect of reality versus artificial testing... challenge of not real world testing capacity...repeat quote see above*] [16,F,4,I,M_G]

Mismatch of tests with reality

...[16,F,4,I,M_G] parents suggestion 'aim is to mimic reality' I think so, and I think you could by parent's videoing. If you say what the things that you want to see are, and then if we video it at different times, because we observe, I observe-, even though with her last Botox assessment it was very good, I was actually shocked in the room at how straight she could walk and how well-aligned it was, even though we do the warm-ups every morning and that's why we do it. However, actually, her tripping and her falling is much worse now. There is tightening. Yes. Then she's been falling as much whereas you didn't see the current situation, the real, current situation....[16,F,4,I,M_G]

Goal setting (Test_goals)

Do you feel like you got the chance to actually think of goals that were important for X and for you? Yes. It was just like he leads a normal life without it affecting him, as much as we can really. [56,M,9,II,M_P]

[Do you feel like you've been able to set goals that are import to you and to your son?] Yes, because you set goals but you actually achieve them, which is really good in that sense. I'm just so happy that we did persevere with it and keep getting it done because-,. ..[7M12M_G]

....the first two times he had it done, amazing fantastic. The third, which I would score ten out of ten, the third time I didn't see a significant amount of change, on the third time, but nothing too..., maybe it just got used to it, or I'm not too sure, but I'm not too sure. . In the sense of ...so I think you're at a pace because the first time and second time you can see things moving, and then, the third time was less. Maybe he got to the goals and everything by then. But the fourth time we did something different, I remember when you did the hamstrings, and then we were like, wow, because you took the extra mile, he's done his running, he played his football, and it was fantastic[7,M,12,1,M_G].

I found it very hard to set the goals anyway Because at the end of the day, I just want her 100%, and it's hard to actually rate, but yes, I just, yes, I found it, yes, it was quite hard to.. Yes, especially as they get older. You know, because she always hears. She's that bad. You don't even realise she's heard, and you're like, oh okay...**It comes out later...**F: But yes, you're quite mindful to always be positive, but, yes, it's quite hard to. [63,F,5,II,M_M] [*mum talked about hard to talk about shortcomings and areas of difficulties in front of the child when setting goals*]** ..

Yes, I found that quite hard. Yes, they (*local team*) do (*talk about goals*), ..I think they get sent the letter as well and they come -, so after the injections, we normally have the six-week block when they try and work on the things that are his goals, yes-, [19,M,6,M_M]

Dad: yes, and actually, like, so, for example, just explaining, 'Okay, we're going to do the hamstrings because we want to try to improve the sitting posture, improve the heel strike,' so these, to me, are goals. They're like, 'Okay, we expect to see a better posture.' Mum: It's good because we know what we, sort of, should be aiming for and hopefully, the outcome... So, the goals are great... we get asked what the main problem is.. and then we-...set the goals together. 33,M,4,III,M_G]

Do you feel like you got the chance to actually think of goals that were important for X and for you? Yes. It was just like he leads a normal life without it affecting him, as much as we can really. [56,M,9,II,M_P]

...thinking about the goal setting. We talked about that before. Did you feel like you had the chance to talk about them with the team here, and also with D? Yes. I know we talked about climbing down the stairs, that's one. I can't remember the others And D (*local team PT*) has been really good as well. As you all ladies have here. [68.M,12,III,M_M]

I feel we might have been a little bit too up there *Ambitious?..* With the standing.(mum) Dad: I don't know because that's the difference. I think that we're on target for the goals. I don't think when we're setting goals, I'm not setting goals for our next set of injections, I'm setting goals that I want to achieve.... Long-term

goals. [70,F,4,III,P_M] *expertise of setting short term and long-term goals requires skillful guidance of team*

Questionnaires (Test_ques)

Well, this is really funny you say that, because I was going to say to you, if you gave me this *questionnaire*) and I only had X, I only had one child with cp. I would feel like I was filling this out and it wouldn't be any different, that all children with CP or not CP were all the same. It was not until I had a younger child that I distinguished the difference for how each child develops, so when you do answer it you notice it so much more because you're like, 'my child at home who's a lot younger, can do a significant amount of stuff at an age where..'-,*[talking about questionnaires and filling it out each time reflecting on how questionnaires made mother think about everyday activities and how the child was affected]* [7,M,12,1,M_G].

It's difficult, I can't pretend I enjoy it,, that said, if it's all part of the research to make it better for future people with this condition, fantastic. A lot of it causes us to think about, what S's reaction to something will be, I can usually take a guess, but I don't know, and that's the inherent complexity and difficulty that one has.In my view, I think it's more, doing the physical stuff with S, and looking at it, and filming it, and looking back at those films to see the progression. That, I think, is more important than some of those questions [62,F,10,I,M_G]

They were very good, they were good, they were well broken down into different areasReally good detail, I think the right questions were asked. It was really about the quality of life, it spoke about family and, you know, relationships and area and local community and so on, which I think is really important. Yes, and look, I don't know if these-, it's a good way of assessing progress, and we never got these sorts of questions before.... [33,M,4,III,M_G]

Look, if anything, and this is being a bit picky, but there was no problem filling those questionnaires in, I think it was really nice to reflect back on it. I just think if that was something being considered for, I don't know, more people, then it would be

better to have it slightly shorter because it is time-consuming and, you know, you have to really think about it.... You know, you've got to think about the goals, there's quite a bit of writing to do, but yes, like I said, it wasn't a problem, but I think, if it was to be more for everyone....that comes here, they may not want to do such a long questionnaire. Mum [33,M,4,III,M_G]

maybe just stagger the questions so there are fewer over a course of time or something. Don't get me wrong, I think the fact that we've done them, I think we really appreciated them because it was that reflection of, you know, okay, I haven't thought about this before, and then really, just trying to process where's he improved, what are his goals, how's the local community? Dad [33,M,4,III,M_G]

I struggled with those I find the wording, trying to make sure I write the right answers, they're a little bit, almost, twisted. Like, I was, I had to make sure that right that, yes, I just had to focus a little bit more..... it was just, like, what do they actually mean [63,F,5,II,M_M]

Yes, they've been alright. Some of them, you really, you've really got to think, [68.M,12,III,M_M]

Really trying to push the mundane things, you know, the smallest things like opening a cereal box, those kinds of questions do make you start thinking about, it's not just about doing the physio, the stretches and stuff, it's actually using your hands (*and legs*) in a real-life situation. Opening the cereal, taking it out, putting the bag back in, pouring your own milk, but we started doing all that with him, now. (*child had upper and lower limb injections*) [33,M,4,III,M_G]

Yes. The questionnaires...., it's something that you have to really, really read through. To be honest with you when I do these questionnaires it's about 25 minutes because some of the questions are loaded one way slightly, so you could do a negative when it should have been a positive and vice versa. Some of them don't follow on extremely well. I think some need to be batched in a certain different way, but I understand why it's done, but I think it's just more a case of

when you fill them in, it's not to do it quickly you have to give it a hell of a lot of thought. A lot. [66,F,4,III,M_P]

Oh yes, well they ask about obviously how my child feels and how he copes and how he manages (CPQOL). Yes, pretty self-explanatory. Because some of them do say, like, mall, and they are worded (PEM-CY). Its either I'm getting used to it, or the English grammar is a little bit better. This one's better than the last one I did, or the one before. . I definitely think it's worth doing. Because you can get a better understanding[7,M,12,1,M_G]...*feedback re Australian and Canadian Ques*

Yes, some of them can be a bit long-winded. Yes, some of the questions are a bit repetitive as well, yes. and some of it wasn't really relevant. (PEM_CY) CPQOL Okay, yes, I preferred that one, I think. *Questions re finance found strange* ..Yes, I wondered why that was in there, yes.[19,M,1,M_M]

Yes, I do (*think you are picking up all that's important for us*).... Yes. I think in the questionnaires and stuff, everything's covered. [59,M,6,III,M_P]

I think they're a little dated and I think..., it doesn't really fit what you're trying to do..... I think when you're looking at the scales and stuff like that, might as well just throw a dart at a dartboard but it's okay, that's not an issue [70,F,4,III,P_M]

I would look at the structure of them a little more and refine them and perhaps, instead of focusing in generally and socially, but perhaps you could bring some of your stuff here into it. So, what the experience is all about and stuff like that because I think you'll get a better range of data to perhaps assist [..] you[70,F,4,III,P_M]

I have also presumed because there's a range of children, so therefore it's got to be quite comprehensive but some of it's just not needed. There's no relevance to it. [70,F,4,III,P_M]

I don't think it made much of a difference, to be honest (*would you have preferred to do them online*)..., no.... Yes, it was quite easy because I just did it whilst they were seeing X in the appointment anyway. [19,M,1,M_M]

Timing (Test_timing)

We came here six weeks after the botulinum and they measured him, so it was about the same....then (*at six months*) we saw the improvement in that stretching... then (*at 12 months*) he's maintained every single injection he's had, he's maintained the range of that stretch. [33,M,4,III,M_G]

it was quite nice actually, yes, just to see how he's getting on in that in between stage, yes. *Extra 6 month appointment* [19,M,1,M_M]

Yes, I think it's reassuring (*extra appointment at 6 months*). And if you've got any problems, you know that it's not going to be too long until you're seen again so you can express what the problems are. ...Personally, I think it's reassuring to come because for me you could ring me and say, 'How's he getting on', and I'd say, 'Yes, fine.' But then, I might have missed something and then, when you see him, you might go, 'Yes, but his arm shouldn't be bending that way.' You know, or whatever. I don't know. I think it's better to be seen[59,M,6,III,M_P].

Parent suggestions -Testing (Test_parents)

Yes, I mean I am always asked how he's getting on and loads of stuff. I mean, I don't think I've ever been asked, until today, how he feels mentally. It's always been quite physical, which is obviously understandable because that's the aim of the thing. But then, to be fair, I think he's only just reached that age where it would start affecting him maybe more, But I think it might be good to just maybe ask, you know, how the child's feeling, because some parents might not bring it up. Because they might not feel like it's relevant [59,M,6,III,M_P] [*important to ask personal factors...questionnaires addressing all areas of child's life*]

I probably could do more with and persevere with it a bit more is cycling, so I don't know if you guys (*GOSH*) ever had like a cycle bike, I don't know if it's the same that he could maybe test now *when asked if we could support more and do different tests ..suggested bikes* [7,M,12,1,M_G].

maybe riding a bike, that would be a good one, because that's a different movement because it's a push against. [51,M,5,II,M_G]

I think (*tests*) they're at your limit though, if I'm honest, like, when you do, jumping from one-, you do put your all into it, don't you? The jumping and the walking along the line[62,F,10,I,M_G]

I'm not sure (*about extra things to test*) but the only things, well I think.... Maybe like balancing when maybe jumping different sorts of ways and that. ..they have to think of harder stuff because I am so good at it! [51,M,5,II,M_G]

BoNT-A Treatment

Physical change_positive (T_positive)

I've been blown away with the Botox, I really am. [68.M,12,III,M_M]

there was a drastic improvement to what we saw after we had the injections. So, there was a change in her, physical, handling, everything else, she just seemed to be starting to do different things. So, I don't know if that means her body was more relaxed or more responsive or whatever, but there was a difference from that point onwards[70,F,4,III,P_M]

I mean, if you would have told me three years ago that she'd be that well, I would have been so gratefulwhen we're not expecting that, it's more like that we think, 'Right, okay, let's keep this going everywhere.' We are really, really pleased with the results, so for us it's made a massive difference, [1,F,5,1,M_G]

I think also that even something as advanced as a botox injection is even available for something like this (*GMFCS I*) was just really encouraging, I thought. Then it

was, yes, so we are a massive advocate. [1,F,5,1,M_G] *Parents think child very mild so wouldn't have been eligible for this 'advanced intervention'*

Look, he's got, obviously, he's got a way to go, but it's not that, it's, like, trying to get the best out of him, the best that he can be (*Reach his potential*). The best he can be, yes, and I think he's doing amazing, I mean, we're pleased with his progress... And he feels very pleased... he does, definitely! [33,M,4,III,M_G]

Participation (T_Particip)

when you've got a child with cerebral palsy that you are so desperate for that child to run around with her peers and have a full life, because children don't stop, they will run and expect you to run with you and if you can't keep up, which she couldn't do, she would just sit in a corner with her head dropped. So for me the participation (following toxin) outweighs everything. [66,F,4,III,M_P]

She wants to do things, she wants to walk. She knows she can't, because she knows exactly what she's got, but she's just got more determination at doing *things* [70,F,4,III,P_M]

But he's doing things now that weren't possible before the injections so there has definitely been an improvement. So, before, just to jump he would struggle to get both feet off the floor, sort of an inch. Now, he can, say, jump off the step. He can't jump up a step but he can jump off the step, you know. Like while the injections were at their strongest, like the effects from them, he was just walking off the kerb, up the kerb, you know, no hesitation, no worry [51,M,5,II,M_G]

She's more mobile in her walker, which is brilliant, because she can actually run around in the playground with her friends. So she's getting more confidence to build friendships[66,F,4,III,M_P]

First thing I noticed was, where I walk with him. And I have to support him underneath, usually. Or hold two hands. And so, he can walk, just holding one hand.

To the car and back. And just how much more stable he was. And not wobbly[68.M,12,III,M_M]

Just after (*injection*), it's like it makes them (*muscles*) worse [51,M,5,II,M_G] Because, obviously, they seem to become a lot weaker, but then the physio kicks in, and We'll see him just doing something small, wasn't it ..Mum: Yes, like he'd start jumping. Dad: Like he just does it, rather than more thinking about doing it. [51,M,5,II,M_G]

I remember when you did the hamstrings, and then we were like, wow, because you took the extra mile, he's done his running, he played his football, and it was fantastic [7,M,12,1,M_G].

Skipping, he's done skipping, after he done the Botox before, he managed to conquer skipping didn't you,? ...he's doing swimming religiously every week.. [7,M,12,1,M_G].

I've noticed that her running is a lot better, she is running a lot more... It's not so uncomfortable for her to run she does do more walking.. [3F,4,1,M_M]

She does swimming. She does gymnastics lessons. tennis and swimming[16,F,4,I,M_G]

And I think, if she wants to do it, she will do it. Even if she'll have trouble, it doesn't bother her, she will get on[63,F,5,II,M_M]

M:Definitely, I think, cycling has even become easier. Yes, so we've got this track, a 400m track near where we live, and it's good because it's a flat surface. So, I think initially, with the bike, I mean, we would barely get halfway and then we'd need to push him and stuff, and now, at this point, he's doing, like, three laps. F: In six minutes each, you see, so that's quite an improvement[33,M,4,III,M_G]

But he's able to stand and do two things. If I told him to stand and play with the iPad, he's able to hold it (TC: 00:10:00) and do that standing, he's able to now hold a glass of milk and stand and drink it. [33,M,4,III,M_G]

Yes, kicking a ball, he couldn't kick a ball before, but now, he's able to kick a ball and stop. [33,M,4,III,M_G]

[*better walking up stairs*] ..Stairs were easier..... fall over less [62,F,10,I,M_G]

..... This was a full day trip, you .., got into London, and then did Seven hours (*walking on a school trip*).... before she had the Botox, she'd have to have a buggy, [62,F,10,I,M_G]

Like he'd now jump off the front door step..... like he'd start jumping. Like he just does it, rather than more thinking about doing it. [51,M,5,II,M_G]

But he's doing things now that weren't possible before the injections so there has definitely been an improvement. ..before, just to jump he would struggle to get both feet off the floor, sort of an inch. Now, he can, say, jump off the step. He can't jump up a step but he can jump off the step, you know.he used to walk when he was going across a road he'd stop dead, one foot, two foot, and then cross the road, get to other side, one foot, two foot, but while the injections were at their strongest, like the effects from them, he was just walking off the kerb, up the kerb, you know, no hesitation, no worry,. [51,M,5,II,M_G]

Yes, he wasn't enjoying swimming at all (*before injections*), and it really took his confidence because his friends were at a different stage to he is, and he found that quite hard. But, I think now, he feels more able and it's given him a bit of confidence as well. He just goes for it now and tries his best[56,M,9,II,M_P]

do the 2k junior park run. [63,F,5,II,M_M]

It's a shame there is no long term scale of how it (*toxin*) affects you later on life, that's the only, that is the downside, but when you've got a child with cerebral palsy

that you are so desperate for that child to run around with her peers and have a full life, because children don't stop, they will run and expect you to run with you and if you can't keep up, which she couldn't do, she would just sit in a corner with her head dropped. So for me the participation outweighs everything. [66,F,4,III,M_P]

First thing I noticed was, where I walk with him. And I have to support him underneath, usually. Or hold two hands. And so, he can walk, just holding one hand. To the car and back. And just how much more stable he was. And not wobbly[68.M,12,III,M_M]

School are pushing him harder, daily mile... frame football... Swimming.... (He is) Faster, better. [68.M,12,III,M_M]

suppose, we're walking him to, to there, and we'll get near it and he'll go, 'leave me, I can do it', and he'll walk the last couple of bits, which we keep telling him off for it! [68.M,12,III,M_M][*increased independence*]

Yes, at school, she'll stand at the school table... ... participating more than she was.... She wants to stand a bit more, so, yes, I think in that way it's helped. [70,F,4,III,P_M]

Look, he's got, obviously, he's got a way to go, but it's not that, it's, like, trying to get the best out of him, the best that he can be [*Reach his potential*]. The best he can be, yes, and I think he's doing amazing, I mean, we're pleased with his progress... And he feels very pleased... he does, definitely! [33,M,4,III,M_G]

Participation Challenges (T_partic_chall)

We've been trying to get her into clubs, but because she's only in year one at the minute, it's a struggle to get her into the clubs and a lot of money Because the ballet, she found hard, so yes, we want to get her into street dancing.....we try and take her swimming as much as we can. [3,F,4,1,M_M]

Endurance (T_end)

I think the other thing is endurance, you know, there's an improvement in that ... His endurance has improved massively. I would say from this time last year to now, amazing, that improvementHe's changing and growing, he's on medication, Botox, physio, so all of these factors, I think, play into it. But I think, for sure, from our perspective, the Botox has helped. I think it's almost like the first time he had the Botox, we felt like he was at a plateau, and this just gave him a little bit of a boost. [33,M,4,III,M_G]

Well, she's not on her tiptoes, like, she doesn't get told to get off her tiptoes as much She can go (*walk*)longer now. She doesn't get pains in her legs. She's pretty active. Like, her twin sister is likely to start moaning about being tired before she will. [37,F,5,I,F_M]

He can actually stand up and walk,.. it (*environment*) does matter because your day-to-day getting up and about and so, yes, no now you can see how he's benefiting from the Botox, from the physio. Because he is now, he's at a nice pace[7,M,12,1,M_G].

Timing of response (T_Respon_time)

The tense nature of her ankles eased straight away, almost, when I say immediately, it wasn't immediately, but in a period of weeks, you could a different relaxed position of her ankles. And I was quite surprised how quick that worked.

[70,F,4,III,P_M]

I wouldn't say you see any difference overnight, but it's when you-, all of a sudden you sort of think back a few weeks and you think 'they couldn't do that'. .

[51,M,5,II,M_G]

Yes, so it wasn't even, you know when they said, because our local physio said it takes two, three weeks. We didn't see it straight away, like I said, it was a good, I would say three months in, then you could see that they had actually numbed the muscles that they were planning to numb.....I think just the stretch, like, you know, just the flexibility (*was easier*)I think following the injections, there wasn't that much of an initial difference, but I think we just persevered with the physio, and I

think over the weeks, there was definitely an improvement. Yes, it wasn't immediate. So, it's weird, I don't know if that's what's supposed to happen, but it was over that chunk of time. [33,M,4,III,M_G] *DELAYED RESPONSE TO KICK IN*

He definitely had a bit more motion. He could move about a bit more easily, It has lasted for quite a while, yes, because I know the effects only last for six weeks but I think it does last a lot longer than that. In the long run, yes. [19,M,6,M_M]

Then it took another few weeks to really kick in, but it was really gradual, which was great in a way because she could adjust to it slowly.....a massive change.: Yes.

Massive. Yes [16, F,4, I,M_G]

ADL (T_ADL)

Yes ... little things actually, I remember when he had the Botox in his arm, he managed to do his zip up, he managed to do his buttons up. When he had the first lot of injections in his leg, it was so much easier to get his shoe on his foot. [7,M,12,1,M_G].

She's more confident climbing stairs now before, she wanted someone behind her all the time, whereas now she'll do it herself.. [3,F,4,1,M_M]

X started to be able to go up and down the stairs. [51,M,5,II,M_G]

BSF/Pain (T_BSF)

He was really tight, and especially how he walks was quite tight, how he walks, and he's loosened up quite quickly. Yes, his foot used to be very turned in, even with the splint on, [56,M,9,II,M_P]

Pain (T_BSF_pain)

When she's walking...she'd said it's really, bad again... ..Yes, last two months, she's been moaning more about her leg, yes (~10 months post injection). So, I'd say... it's lasting a lot longer this time.... it (*the effects of injections lasting*) was about seven to eight months it was lasting last time [3,F,1,M_M].

He does get pain in the back of the knee (*at night*). I think it (*BoNT-A*) does help a bit with that It's mostly when he's done a lot more activity than normal, and it's not every night [19,M,1,M_M]

Yes, it (*the pain*) reduced. It never went. I mean we don't get pain every night, but like, there was less of it, there was less episodes of it. But generally, it's if he's had a really busy day and then we have pain. The injections definitely reduce that part...Before (faces pain score) was seven or eight out of 10.. at six weeks Probably about two It was creeping back up towards a three, yes. It was just starting, you know, like, to worsen after six months [51,M,5,II,M_G].

Weaker(+/-) (T_weakness)

Just after (*injection*), it's like it makes them (*muscles*) worse [51,M,5,II,M_G] Because, obviously, they seem to become a lot weaker, but then the physio kicks in, and We'll see him just doing something small, wasn't it ..Mum: Yes, like he'd start jumping. Dad: Like he just does it, rather than more thinking about doing it. [51,M,5,II,M_G]

Mum...She was a little bit unlucky. The last one she had, because she had serial casting after, and then we went on holiday. So, there was a heatwave in Portugal, so it was really hot, she had really weak legs, it was just a bit I think it just, because it made her legs weaker, and then obviously we went straight into a summer holiday. She came out of the plasters on Thursday and we went on holiday on the Friday. [37,F,5,I,F_M] *toxin and casting*

Stability (T_stab)

I don't feel any difference, but for her, she's more steady. Even when she's on her splints, she's much more steady after her Botox.Steadier, more confident. Much more competent... it gives her tons of confidence.... eight weeks (muscle softness lasts) ...but the confidence lasts much longer. [66,F,4,III,M_P]

Confidence (T_confid)

[Toxin has had a positive emotional knock on effect]..... because the frustration when she would hit herself in the head, it's like her head didn't work and she'd slap her head to make her head work. She hasn't done that for months. No the only time she ever asks me is why doesn't my legs work?

[66,F,4,III,M_P]

She's more mobile in her walker, which is brilliant, because she can actually run around in the playground with her friends. So she's getting more confidence to build friendships [66,F,4,III,M_P]

Yes, he wasn't enjoying swimming at all (*before injections*), and it really took his confidence because his friends were at a different stage to he is, and he found that quite hard. But, I think now, he feels more able and it's given him a bit of confidence as well. He just goes for it now and tries his best[56,M,9,II,M_P]

I don't feel any difference, but for her, she's more steady. Even when she's on her splints, she's much more steady after her Botox.Steadier, more confident. Much more competent... it gives her tons of confidence.... eight weeks (muscle softness lasts) ...but the confidence lasts much longer. [66,F,4,III,M_P]

This is making him so confident[68.M,12,III,M_M]

it's never an easy decision to put your child to have more injections in their leg and all of that, but there's no downside and I think that's the important thing. We've seen no, nothing that's negative from the Botox. If anything, even though it is short-lived, that confidence takes her through many months. [66,F,4,III,M_P]

she must feel more comfortable with it. More confident [70,F,4,III,P_M]

and I think he's more confident now and he's more happy now. He's not on the floor every ten seconds. He can actually stand up and walk [7,M,12,1,M_G].

Experience of Treatment

Procedure (E_Btx_pro)

I thought everyone was very friendly, it was done quite efficiently...I think she wasn't, I don't think, distressed. She was actually quite looking forward to it. So, yes, no, I think it was only the bit, I think, when the actual injection went into her thumb that she cried. ***(That's a very painful one)***, Yes, that's what they said. So, and apart from that, everything, she enjoyed the whole day I think. I think it was -, she had been looking up to it and telling everyone, 'I'm going to have my Botox.' No, no, she talks about her Botox quite often. Any time any hospital gets mentioned, 'I've been to hospital, I've had my Botox.' And it's a proud -, yes, she wears *(It's a positive experience?)* : Yes. Nothing put her off from it, so, and we talked about, obviously we didn't know what was going to happen, about coming back to have it again, and she seems fine. [63,F,5,II,M_M]

All of it, fantastic. More than enough information. The whole procedure itself, the care, you, I mean, this isn't just one person, there's like a team of five the whole time, whether they're the play or they're the physio or you or anyone, I mean, surrounded by professional care. I feel it was a perfect experience. What we have learnt from this though, with X is because obviously the last time she had it, she decided to-, the anaesthetic to work not until she'd actually had the procedure, which kept her asleep for hours. [66,F,4,III,M_P]

Well, they said it has an amnesic, which I hope it did. So, she just had a good time and she says that.. she can't quite piece it together, and we think that's good. [16, F,4, I,M_G] (A_Pro) (E_pro)

It's also the hospital. I mean, you just see the experience that the physios, nurses, the way things are, the way it's set up, it's just amazing. [1,F,5,1,M_G] *staff*

[Is there anything we could do differently to make it better for the kids?] F: There isn't to be fair, no there isn't because the team are so lovely and friendly, I do think the team are really lovely and friendly, and I've never honestly left once, the unit or the hospital or the ward, and thought, 'oh what was all that about today,' I never

have. I am really, really pleased with how everyone has been with M.

[7,M,12,1,M_G].

So, the actual process of having the injections was amazing. It couldn't have been more brilliant, and you can see that she's almost not conscious about it's happening[16, F,4, I,M_G]

Yeah really good [*injection experience*]The young girl [*play therapist*] was talking to him. ...

He didn't even know he was having it done. He was waiting for them. .. He never knew he had them. He asked us when he came out. 'I thought we were having injections'. ..the young girl was talking to him and she had the little laptop thing, and she was asking questions ...And he's totally focused on that because he wants to say the right thing, doesn't he? Because he wants to impress her. And seriously, he never knew nothing.... he was so concentrating on the (game), he didn't even flinch. [51,M,5,II,M_G] PROCEDURE

When you take her in, she's-, you're really good with her, when she's in there the play person is really good. We have story time, don't we? Because you're a bit wobbly. [3F,4,1,M_M]

I think the thing that we appreciated was the dog therapy, I think it was a small thing, but he really enjoyed it and it just comforted him..... she (*play therapist*) let him watch something he wants to watch, so to be fair, he was watching it and having the actual injection didn't impact him... he was so focussed on watching that, he forgot what was going on at the other end. [33,M,4,III,M_G]

Parental Expectations (E_Parent_exp)

Just after (*injection*), it's like it makes them (*muscles*) worse[51,M,5,II,M_G]

Because, obviously, they seem to become a lot weaker, but then the physio kicks in, and I wouldn't say you see any difference overnight, but it's when you-, all of a sudden you sort of think back a few weeks and you think 'they couldn't do that'.

[51,M,5,II,M_G]

I didn't really know what to expect. It was just a wait and see sort of thing. I wasn't really sure what would happen. There was no point of view, and that's what it did, so.... I think it's definitely worth him having it. He benefits for a while it's easier for him. [56,M,9,II,M_P]

If you'd asked me a month ago, I'd be going, 'I'm not sure,' I would still be hesitant because of matching our expectations and seeing the reaction, but I think as time progresses, I can see how that has affected her for the positive, to a great extent.

[70,F,4,III,P_M] *IMPORTANT PREPARING FAMILIES FOR EXTENT of change / MANY CASES MINIMAL CHANGE POST INJ**)

Because I suppose I'm a little bit more open to the fact of what she is doing more, what she isn't doing more, so there was a delayed reaction, I must say. At the start, I was a little bit more, well, we've got something but it doesn't seem to be a lot. And there are concerns with other parts of her body which makes it hard to give a real definitive yes or no. So, for instance, she's got really tight ankles and rotation on her hips, so it's not like we wanted, oh right, she's had the injection and she's going to be bouncing around, so it's managing our own expectations and making sure we knew what to expect. And gauge, if you know what I mean? There is no rule, there is no -, you just don't know what's going to happen. [70,F,4,III,P_M]

yes, I did think about that. Thinking about, like, if you relax the muscles, the muscles she's got, is she still going to fall, get upstairs, but really and truly, it didn't affect her at all. [70,F,4,III,P_M] [**preparation /expectations**]

Yes, it did feel like a really big deal before we did it. We were like, 'We're going to experiment with this. It's going to be good for her. We're not sure.' Really, we

were almost less happy to do it, but it was really good. :.... You know, it's all a journey-,....[16,F,4,I,M_G]

I didn't really know what to expect, but definitely it's excelled my expectations.
[68.M,12,III,M_M]

I'd spoken to quite a lot of other moms, and some of them said that it's worked with their children, and some of them said that they haven't seen that much change. So, really, I went into it expecting that perhaps not, not-, but for him it's worked massively. [68.M,12,III,M_M]

I wasn't worried about it, I just wondered how effective it would be. Because I spoke to so many other people-, and they said, 'mm, not, not that brilliant'. I mean, you don't know how it's going to be, because all children are different, aren't they?: They're all different. For him, I think, I couldn't tell you how much I think it's worked for him...: It's fantastic. [68.M,12,III,M_M]

I think don't expect a miracle.... Even if it didn't have that much (of an effect), I'm still glad we did it. [63,F,5,II,M_M]

I mean, if you would have told me three years ago that she'd be that well, I would have been so gratefulwhen we're not expecting that, it's more like that we think, 'Right, okay, let's keep this going everywhere.' We are really, really pleased with the results, so for us it's made a massive difference, [1,F,5,1,M_G]

I think also that even something as advanced as a botox injection is even available for something like this was just really encouraging, I thought. Then it was, yes, so we are a massive advocate. [1,F,5,1,M_G]*Parents think child very mild so wouldn't have been eligible for this 'advanced intervention'*

I felt like there wasn't that much information, actually, about that process at all. I think that's probably because each case is different. So, that's what they say... Each case is different, but it means that you're not prepared as a parent for what

will happen. So, the actual process of having the injections was amazing-
,....[16,F,4,I,M_G]

Experience Negative Parental expectations negative (E_Parent_exp_neg)

No, (*didn't notice negative things first two injection episodes*), We were naïve and we were looking at the positive side [10,F,4,II,M_P]

No, I think the first time we thought he's going to be like jelly, but no, it was nothing like that That's what I expected, but it was nothing like that, he was absolutely the same as it was the day before [33,M,4,III,M+F_G].

Experience Procedure negative (E_Btx_pro_neg)

(*I was hoping*) That it would just, kind of, relax the muscle and help him to move his foot a bit easier so we could at least get a splint on. And maybe to try and stop him falling over as much, really....(*instead*) He did struggle... It was quite a few weeks.
.[59,M,6,III,M_P]

[*were you worried about him having the Botox the first time?*] Not really, to be fair, because with operations it's different. I am worried about that, but I think it was more just wondering what-, I didn't really understand what how a needle was going to make a change in his arm, but it did. I didn't think it would in his leg, to begin with, to be honest. I did have a bit of hope, but I wasn't expecting that because I just thought his leg was just past that point anyway, to be fair. [59,M,6,III,M_P]
mum felt leg was too tight to make any difference child went on to have surgery before T3

We knew it was only a 50/50 chance of it working...Yes, because they said her muscle tone was very extreme. [60,F,6,II,M_P]

The only negative thing I noticed is he kept complaining of back ache (*in bed*), but only lasted a couple of weeks[68.M,12,III,M_M]

Yes, it was so bad, we said we didn't actually want her to have the injections done again.....[did try again reinjection within the study], but then obviously they got offered the injections in a different place and not as many places, and then the casting, so we said alright we'll give it one last go. To be honest I'm neutral on it now, if you'd asked before, when it was going great,... I would said I loved it, brilliant, and then if you'd asked me the last time I would of said really don't like it, but it's- we've had the good and the bad, so kind of neutral about it now : We won't be doing it again. I've had a chat with Dad, and we've agreed that we've tried it twice now, both since, and it's been bad two times, so we've said we don't want to put her through that.. [10,F,4,II,M_P]

What we have learnt from this though, with X is because obviously the last time she had it, she decided to *fight* the anaesthetic *didn't* work not until she'd actually had the procedure, which kept her asleep for hours. [66,F,4,III,M_P]

She was screaming, looking at us, wide eyes saying, 'Mummy, make them stop. Why are you letting them do this? Mummy, make them stop,' she fought the sedation.....as soon as she came out, .. she went to sleep(*I thought*) she wouldn't have a clue what was going on, let alone reaching for me and screaming for me to make them stop hurting her. And she was dreaming about it afterwards and started waking up in the night as wellHer anxiety went mad and she was not having none of it, and I was like I'm never putting her through that again. And I said to her, I'm not putting her through-, especially *as* this time it didn't work..

[60,F,6,II,M_P] **NEGATIVE EXPERIENCE**

The event, the actual event, when we're there and the doctor was there and I think you were assisting or guiding whatever the case is, you did it nice and quick and everything else. But, emotionally, I think it was draining for her, it was draining for me and I'm quite a tough guy, so, but it was very draining for me and I think that has been a flashpoint for her. She will know something's happened there. So, yes, I don't want to, sort of, say, 'Oh, it was terrible.' It wasn't terrible, it was justI think that stems from her mobility, you know, fight or flight, that sort of thing. The

second that she goes, 'Actually, I'm in a position and I don't know what to do,' that's it and you've got that freezing, kind of, situation. -, [70,F,4,III,P_M]

I don't think anything we do is going to change it, no... (*[preparation on the injection day]*) She's set in her way,, she cried last night because she didn't want to come here she said, 'It hurt, blah blah.' I had to convince her that we were only coming here today to talk [70,F,4,III,P_M] -, [70,F,4,III,P_M]

[future plan?] You just have to do it, she will scream, she will cry. I don't think she's going to take the medicine like she did before, she's shocked us, the nurses said, 'Take this,' bang, bang, done.And she did it and that's rare. This time, I think, because she knows what's coming, because, to be honest, really not sure the sedation what it did, because she still screamed in there. Obviously, it must have numbed it a bit, [70,F,4,III,P_M]

it's the wait, it's the anticipation, that is not good for her. [70,F,4,III,P_M]

Mum...She was a little bit unlucky. The last one she had, because she had serial casting after, and then we went on holiday. So, there was a heatwave in Portugal, so it was really hot, she had really weak legs, it was just a bit I think it just, because it made her legs weaker, and then obviously we went straight into a summer holiday. She came out of the plasters on Thursday and we went on holiday on the Friday. [37,F,5,I,F_M]

And, so what was it like in comparison to when you just had the Botox injections, and didn't have any serial casts? Well, remember when you prodded me with the fork? She was putting stuff on the table, and because her legs were weak, she had a fork in her hand. *Luckily* It was Mummy's bum and not Jodie's head! *Weakness even without casting previously..causing trips and falls mum describes an incidence when child fell* [37,F,5,I,F_M]

with that (serial casting pre injection with infected heel sore)and the injection combined, it was six weeks he wasn't walking for. So, he went back to crawling on

his knees.stiffness afterwards was probably a bit worse, but then I put that down to the fact that he hadn't been on his feet rather than the injections. I don't actually think that was because of the injections. [59,M,6,III,M_P]

when her legs were very wobbly that time, was she very upset No, she was alright, after a few weeks she was a bit frustrated more than anything. She obviously went from being able to do stuff to then not being able to, so it's just more frustration than anything.[10,F,4,II,M_P]

It was literally from the minute we left, obviously I know she'd had the anaesthetic....Exactly, so we gave it a few days, just to make sure and she just, that was it, then literally from that day, she just couldn't really stand on them. We couldn't understand, because obviously normally it takes a few weeks for the injections to start working, and then she stayed like that for the whole time, *Did it get worse, more floppy, or not really?:* No it just didn't change, and then gradually she started being able to crawl again and then she was up on her knees, it was gradual [10,F,4,II,M_P].

(Weakness lasted 1-2 weeks)...Yes, I'd say by the time his physio-, his physio had started two weeks after, and I'd say from by the time his physio finished, any signs of any weakening were gone. [51,M,5,II,M_G]

Side effects: He had a few, like, where he wet himself. *Immediately?* No, after a few days. But it wasn't so much that he didn't realise, he just wasn't able to hold himself as long.

He was just leaving it too late. Take it for granted how long he could hold himself, you know. So, and then finding he was caught short. *How long?* Just days and then I think he's adjusted himself and realised, 'Actually I need to go as soon as I need to go.' [51,M,5,II,M_G]

yes, her legs *do* feel softer in the calf muscle but you can't feel the muscle, if you know what I mean. And they said, in her legs, it did work a little bit better on her

hamstrings because she had more of a stretch but that, especially the left one, it didn't do nothing [60,F,6,II,M_P]

change it was minimal. Absolutely minimal, not worth *Did it make anything worse?*
No, not that I'm aware of [60,F,6,II,M_P]

...And then it didn't work, so I felt even worse, because we put her through it thinking this is going to benefit her. It isn't about what we feel, it's about what's good for her, and then it didn't benefit her at all. [60,F,6,II,M_P]

First time vs repeated injections (E_Rpt)

[Do we ask parents what they feel or do we rely on impairment measures families have clear ideas when it has worked and not worked and if they want to do it again]

Positive (E_Rpt_pos)

[Would you say that this set of injections has been as good as the first set, or better, or the same?] F: I think at least as good, I would say. Definitely.... Yes, and I'm really glad we didn't stop after the first. I think that was excellent. ...The first one really made a big difference, but then the second became-, I think with the second it was just better, the growth, the more confidence, the learning how to swim, and the injection just all came together. How to know what proportion, but it just felt really, like, 'Voom,'. . [1,F,5,1,M_G] **(E_Rpt)**

...the first two times he had it done, amazing fantastic., which I would score ten out of ten, the third time I didn't see a significant amount of change, on the third time, but nothing too..., maybe it just got used to it, or I'm not too sure, but I'm not too sure. . In the sense of ...so I think you're at a pace because the first time and second time you can see things moving, and then, the third time was less. Maybe he got to the goals and everything by then. But the fourth time we did something different, I remember when you did the hamstrings, and then we were like, wow, because you took the extra mile, he's done his running, he played his football, and it was fantastic[7,M,12,1,M_G].

A hundred million percent. A hundred million percent, because I think if we didn't carry on, we would regret it. Because I don't think we would have conquered half of the stuff that we have.....No, I couldn't recommend it enough, I feel so lucky and so grateful [7,M,12,1,M_G]..when asked about whether they were happy with repeated injections

[Less response each time ?] No, there is more response [with each injection] ...See, with her P.E. at school she's doing a lot more, she has a lot more confidence in the P.E., so she's a lot more, doing the balance beams and things like that, she's a lot more confident. She is trying more. She does outside games now as well, with Game On, which is her football thing [[3,F,4,1,M_M].

I feel it's worked a bit better this time. I don't know if that's because it's built up a bit, or-, I'm not sure. Yes, it does seemed to have worked quicker and more effectively. [56,M,9,II,M_P]

I don't feel that she would be as strong if she hadn't have had the Botox (*has had 5 injections*), she wouldn't have been able to get as strong, and to be as normal, to be with her peers and doing what they were doing. [62,F,10,I,M_G]

And I know that, as they get older, they get stronger anyway, but I think that the Botox has helped S in achieving that a lot more, do you see what I mean[62,F,10,I,M_G]

I think the more she has it, this'll be the fourth time. When she had her third time it lasted a lot longer than the first and the second time....: So I'd say the last couple of months has started to wear off and she started to notice struggling more..(lasted 10 months) [3,F,4,II,P_M]

What we have learnt from this though, with X is because obviously the last time she had it, she decided to *fight* the anaesthetic *didn't* work not until she'd actually had the procedure, **which kept her asleep for hours. [66,F,4,III,M_P [reflections on anaesthetic experience for next time]**

The first time was very good, it was really good. We noticed lots of differences in X.
Second time I don't think we got a lot out of it and maybe that was physio's fault,
maybe her body just did not accept it this time. [66,F,4,III,D_P]

[Unsure any difference/no better](E_rpt_unsure)

In his leg, I just didn't see-, I actually noticed he was falling over more. I noticed that
he fell over more after having it done the first time, and then the second time it just
didn't change anything. The stiffness was exactly the same as it was
before.[59,M,6,III,M_P]

I don't think she lost it (*previously gained skills*) as such, but I don't think she gained
anything extra.(*with second set of injections*) [66,F,4,III,D_P]

So, I think it's difficult to compare, I think, because it was different, but yes, I think
overall, the first one felt like a bit better...But again, it might be that because the
first one went so well, maybe my expectation was actually, this is going to be, like,
the next really big leap, but I think it is a gradual improvement rather than anything
33,M,4,III,M_G]

I think there was a better response on the first.....Yes, how the muscle felt. The
second was very, like, I thought it was a good progress, but maybe our expectations
were a little different [33,M,4,III,M_G].

It wasn't as effective as the first one, but I do base that on the fact that there was
no follow up from physio after that treatment, which I think is paramount to get the
maximum successObviously on the first one we had-, by the time we'd actually
got to the ground floor, exiting the building, her heels were on the ground already.
Within that one hour. [66,F,4,III,M_P]

Negative (E_Rpt_neg)

Yes, the first two worked, - She started walking.....she managed to put her foot down a lot more and she was a lot more flexible. but then it (*third injection*) didn't work at all. Like, really no improvement..... She was worse, after she'd had it done she couldn't walk at all for nearly three weeks. - [10,F,4,II,M_P]

The first time was very good, it was really good. We noticed lots of differences in X. Second time I don't think we got a lot out of it and maybe that was physio's fault, maybe her body just did not accept it this time. [66,F,4,III,M_P]

Because it lasted like three months last time and when she first came out of the serial casting the first ever time, it was so nice so I was like, right, although we didn't want to put her through it, if it was going to benefit her then it was worth putting her through that. And this (*second*) time, I was like I'm never doing that to her again because it didn't even have the benefit of-, her foot getting to touch the floor and she (*only*) had a two-week casting because her skin started to have a reaction to the plaster so she couldn't have it for three weeks. [60,F,6,II,M_P] *good first response bad second response due to upset during procedure and no change post inj now had ortho surgery*

Adverse Events (E_AdvEven)

She was worse, after she'd had it done she couldn't walk at all for nearly three weeks. - Obviously she lost bladder control as wellabout three weeks that did. Obviously once it started kicking in properly, and then wearing off then she started getting movement back. [10,F,4,II,M_P]

..kept on needing to go to the toilet, quite a lotreally sudden, he just got to go (*Child*): I just like dash to the loo. [56,M,9,II,M_P]

There was a little wobble in the first seven to ten days, but then ...after that, she was upstairs, everything. [70,F,4,III,P_M]

Toxin wearing off (E_Tox_wearoff)

It's not back to how it was pre-Botox, but it's different, and I think-, because obviously that (*tight muscle*) was kind of switched off for a while, and the switching off is a really gradual thing, and that's why it's hard for her (*child*) to answer that question, because she's actually not that aware, because she has that same outlook, whether it's difficult or easy. She'll say things like, 'Mummy, I'm really wobbly.' That's what we notice. 'I'm really wobbly. I feel shaky.' She won't be as confident with her balance in tasks, but she has the same outlook, whatever (*GMFCS I*). She doesn't have that awareness yet, but we could see the difference when suddenly it kind of went back. However, it's different ... because before, she wouldn't be stumbling over this foot. So, it's almost like now she's programmed that she's got more of a sense going forward, but the foot is getting in the way of it. -,....[16,F,4,I,M_G]

However, actually, her tripping and her falling is much worse now (*toxin worn off*). There is tightening. Yes. Then she's been falling as much whereas you didn't see the current situation, the real, current situation..... No. It's not back to how it was pre-Botox, but it's different....[16,F,4,I,M_G]

it's just starting to wear off, like curbs, he used to walk when he was going across a road he'd stop dead, one foot, two foot, and then cross the road, get to other side, one foot, two foot, but while the injections were at their strongest, like the effects from them, he was just walking off the kerb, up the kerb, you know, no hesitation, no worry, but now he's started to hesitate again... Yes, it was quite sudden ...Quite a quick decline, sort of thing (*at 10 months post injection*). .. he has had a growth spurt. ... wasn't gradual, ...It was more of ...sort of, all of a sudden... [51,M,5,II,M_G]

first injection REFERS TO PERFORMANCE BEING AFFECTED NOW WORN OFF

I don't think she lost it (*previously gained skills*) as such, but I don't think she gained anything extra.(*second set of injections*) [66,F,4,III,D_P]

everything's just getting a bit tighter....[19,M,6,M_M]

Toxin how long it lasts (E_len)

It (*the effects of injections lasting*) was about seven to eight months it was lasting last time and it's lasting a lot longer this time. [3,F,4,1,M_M](

Every time he's definitely had a good improvement... Yes, a good few months, I'd say... I think it was after six months and they said his range was still just as good as it was.... I don't think it's reduced (*in effect*).., I just think that he's not needing it so much in his leg at the moment. That's all it is, yes. the improvement he gained the first couple of times he's maintained-, [19,M,6,M_M]

Experience with family school etc (E_others)

I think, there's not enough -, nothing that they (*teachers*) noticed.

[63,F,5,II,M_M]

Advice to other Families (E_AdvFam)

I think, the same as X, their legs are really tight or and part of their body's really tight, and their finding difficulty within pain. I would definitely recommend it to them. [56,M,9,II,M_P]

You don't know something's going to work unless you try it, and if it doesn't then you don't do it again. But you're not, you know-, if they get harmed in the process, and it makes them worse, at least you've done it with the intention that it was going to make them better, if that makes sense. [59,M,6,III,M_P]

Yes you weigh up the pros and cons. and if it does go wrong, that's not your fault. You did what, at the time, you thought was best. But, yes, unless you try you don't know. [59,M,6,III,M_P]

Every child's different with cerebral palsy. Every case is different with cerebral palsy. If you've got a mild tone, then I'd definitely give it a go. But if you've got extreme tone, I wouldn't bother. Which sounds awful and I wouldn't want to say that to any parent but depending on the tone of their child, I'd imagine-, because obviously if it does any beneficial to someone that hasn't got as much tone, it could be beneficial to them and absolutely, go for it, because seeing your kid's foot or limb go limp after watching it be stiff for so long is a beautiful feeling. But then when you've got your heart and soul set on that again and then it doesn't, you feel like a really cruddy parent because you've made her go through that and there's no point [60,F,6,II,M_P]*first time went well second time not went on for ortho surgery*

I would say, it didn't work as well, for G But you never know, each child is different, so, yes, I'd always say to give it a go. I found the whole experience for her-, it wasn't as stressful as I think maybe other people would find it, so, I would recommend it. [63,F,5,II,M_M]

hundred percent, hundred percent (*recommend it*). I would say you've got the bonus of getting some mobility back but you need a really good dose of self-confidence to make any medication work and with the Botox that gives you the self-confidence to make the drug almost go beyond it's lifetime limits and that lasts for months and months and months, even if the drug wears off in two months time. [66,F,4,III,M_P]

It's always worth a try and I would recommend everyone, the same way we've since met parents who've had Botox and they recommended it hundred percent and our paediatrician always told us about the Botox it's not really a high risk thing, so erased any fears. [66,F,4,III,M_P]

Timing of treatment (exp_timing)

I wanted it done before school so that when she went into school, she didn't feel as restricted, which seems to have worked.: But you don't know what the side effects are, and back then, we didn't know. Because they said something about they can lose control of their bladder, but ..she was fine...there were no adverse effects. [70,F,4,III,P_M] **TIMING**

Adjunctive treatment (Exp_Toxin_plus)

I think it's very different, isn't it? It depends on your ability, so I think S is so, physically active, that, you know, she could get her stretches in doing a lot of everyday stuff and she will go on her bike instead of doing physio. Ride up and down our drive, and that sort of thing, so for S that is the best thing, but then there are other children that have it that are not quite so abled or want to do those things, and then stretches, perhaps, is more the way forward for them if you see what I mean. [62,F,10,I,M_G]

(SLA does extra therapy post BTx in school) she's good as well, she handles X really, really well..... twenty minute a day thing that she does which is enough.....maximising what we're trying to do [70,F,4,III,P_M]

It's a combination of doing everything and he does the hard work, we do it but as long as your child cooperates and does it, I think that's another thing. Some children may not want to do it (*rehab*), can't do it, but he's been doing it and enjoying it, like, we do everything in play, nothing mean. [33,M,4,III,M_G]

they (local team) had it all arranged so it all coincided, so he had his injections, he got his splints, he got his lycra suit and he got his block physio all at exactly the same time..... I mean, it was manic for appointments, but everything was just all done, to all coincide so we got the maximum out of the injections. [51,M,5,II,M_G]
burden on child and family but positive

Yes. I thought it was great that we had that (*local therapy post BoNT-A*), but I think in terms of goals, in terms of what exactly was done (*rehabilitation*), I don't think there was much precision to it. Maybe that's just how it is. That didn't concern me, but I didn't feel like I knew at the end what had been achieved or what was left to do. They didn't then communicate it back to us, so it was ... whatever, six weeks of follow-up, but there was at the end no communication between the physiotherapist and us saying, 'I'm now done with M, I think she is good like this or like that,' or something. Which, I totally understand why there isn't, but, so, it felt like more like a-[1,F,5,1,M_G], *Goal setting with local team ..? lack of communication with parents ? between GOSH and locals ?*

That's it. They need to have a plan, yes. So, that plan, that's a plan so we know. Otherwise we're just like-,.....[16,F,4,I,M_G] *repeat quote see below discussing local team lack of follow up plan*

[Experience of working post toxin in USA intensive session not with local team following first injection]That whole mind-set after going to the intensive clinic as well, the step by step clinic, they basically said to her, 'Look, we're working on your

leg because you want it to be stronger. We're working on the leg because you want this leg to grow as well. You don't want it to not grow the same as the other.' So, it's just really direct. Then that just makes life so much easier, and then telling the school that they can be direct with her like that. They're like, 'I can say it to her?' It's like, 'Yes,' because otherwise all this stuff is built up around it which will give her a bigger stigma in the future, because she's got to live with it her whole life. So, it's about her having a positive attitude towards it. It's really important. -, Because they're going to have to maintain it for their whole life, and it shapes who they are. A big part of it, also, is the social side of having cerebral palsy, because you might not interact with others as much because you just don't physically put yourself into those spaces.....[16,F,4,I,M_G] *Thoughts about being straight with kids and telling them why they need to do certain things*





Our physio, [*locally following second injection*] They did the intensive sessions around the Botox because they weren't doing it and we were like, 'The Botox is now. Do you want to work with us or not?' Now, we're not going to see them again. Now PT said she might try and put something in, in a few months. So, now it's worked really well and we've had the good result....., and now she's beginning to tighten. Actually, now we've got no plan for her! So, obviously as parents, we've put a plan of how we'll continue to work with her, but-, It's bizarre because-, You invest all this time and energy ...That's it. They (*local team*) need to have a plan, yes. So, that plan, that's a plan so we know. Otherwise we're just like-,[16,F,4,I,M_G] *complaints re no long term follow up no plan following post injection therapy*

Highly positive from M's perspective, but I think it's not just the Botox... You have to do the therapy.... It's everything, it's, like, who you've got around you.
33,M,4,III,M_G]

I also get the six weeks' intense physio as well. Which they start that afterwards. That makes a big difference. That's what you said last time. So I chased it up [3,F,4,II,P_M].

No theme group yetDoubts about effects of toxin or natural maturation? *Mum* I mean, she is a different person and she's had the injections or is that her growing up now? Yes, (*she's*) much happier. (*dad*) Yes, that's hard to tell. [70,F,4,III,P_M]

BMJ Open Protocol for The Toxin Study: Understanding clinical and patient reported response of children and young people with cerebral palsy to intramuscular lower limb Botulinum neurotoxin-A injections, exploring all domains of the ICF. A pragmatic longitudinal observational study using a prospective one-group repeated measures design

Lesley R Katchburian ^{1,2}, Kate Oulton,³ Eleanor Main ²,
Christopher Morris ⁴, Lucinda J Carr ¹

To cite: Katchburian LR, Oulton K, Main E, et al. Protocol for The Toxin Study: Understanding clinical and patient reported response of children and young people with cerebral palsy to intramuscular lower limb Botulinum neurotoxin-A injections, exploring all domains of the ICF. A pragmatic longitudinal observational study using a prospective one-group repeated measures design. *BMJ Open* 2021;11:e049542. doi:10.1136/bmjopen-2021-049542

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-049542>).

Received 28 January 2021
Revised 16 March 2021
Accepted 17 March 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Lesley R Katchburian;
lesley.katchburian@gosh.nhs.uk

ABSTRACT

Introduction Botulinum neurotoxin-A (BoNT-A) is an accepted treatment modality for the management of hypertonia in children and young people with cerebral palsy (CYPwCP). Nevertheless, there are concerns about the long-term effects of BoNT-A, with a lack of consensus regarding the most meaningful outcome measures to guide its use. Most evidence to date is based on short-term outcomes, related to changes at impairment level (restrictions of body functions and structures), rather than changes in adaptive skills (enabling both activity and participation). The proposed study aims to evaluate clinical and patient reported outcomes in ambulant CYPwCP receiving lower limb BoNT-A injections over a 12-month period within all domains of the WHO's International Classification of Functioning, Disability and Health and health-related quality of life (HRQoL).

Methods and analysis This pragmatic prospective longitudinal observational study will use a one-group repeated measures design. Sixty CYPwCP, classified as Gross Motor Function Classification System (GMFCS) levels I–III, aged between 4 and 18 years, will be recruited from an established movement disorder service in London, UK. Standardised clinical and patient reported outcome measures within all ICF domains; body structures and function, activity (including quality of movement), goal attainment, participation and HRQoL, will be collected preinjection and at 6 weeks, 6 months and up to 12 months postinjection. A representative subgroup of children and carers will participate in a qualitative component of the study, exploring how their experience of BoNT-A treatment relates to clinical outcome measures.

Strengths and limitations of this study

- To our knowledge, this is the first published use of the 'Quality Function Measure' to objectively evaluate quality of movement (QoM) following Botulinum neurotoxin-A (BoNT-A) treatment and explore whether any change in QoM translates into changes in outcome within activities, participation and health-related quality of life.
- This pragmatic mixed methods observational study will evaluate response to lower limb BoNT-A injections in ambulant children and young people with cerebral palsy using standardised outcome measures within all domains of the International Classification of Functioning, Disability and Health (ICF) over a 12-month period.
- This study is designed to optimise targeting of BoNT-A treatment by identifying patterns of response to BoNT-A treatment across all ICF domains in order to assist clinicians and families in making informed decisions about future treatment.
- This is a pragmatic one-group study design, conducted from a single tertiary (specialist children's) centre. Participants will continue to receive their routine rehabilitation therapy and orthotic provision at local community level. Individualised intervention parameters may make study replication difficult in other settings.



Ethics and dissemination Central London Research Ethics Committee has granted ethics approval (#IRAS 211617 #REC 17/L0/0579). Findings will be disseminated in peer-reviewed publications, conferences and via networks to participants and relevant stakeholders using a variety of accessible formats including social media.

INTRODUCTION

Cerebral palsy (CP) is the most common cause of physical disability in childhood.¹ Although the initial brain insult is described as static, the effects of the neurological involvement are dynamic and change with time and growth of the child.² Increased tone (hypertonia) is considered one of the primary motor impairments in children and young people with cerebral palsy (CYPwCP)³ and a significant contributor to secondary musculoskeletal impairments impacting on activity and participation.⁴

Since the 1990s, intramuscular Botulinum neurotoxin-A (BoNT-A) has become an internationally accepted treatment modality for the management of hypertonia in overactive muscle groups.⁵ BoNT-A once injected into the hypertonic muscle produces a 'reversible' temporary localised muscle weakness by blocking acetylcholine release at the neuromuscular junction. The pharmacological effect is said to last for 12–16 weeks, and the ability of BoNT-A to reduce focal hypertonia in ambulant CYPwCP has been well documented.^{6–8} While the effects can be observed within 24–72 hours following injection, the period of clinically useful relaxation is reported to last between 3 and 6 months.^{9,10}

The progression of dynamic contracture to fixed contracture is a fundamental issue in the care of the child with CP. The period of decreased hypertonia following BoNT-A provides a 'window of opportunity' for therapy to address specific predetermined goals of rehabilitation, such as stretching and strengthening of muscles, increased range of motion of joints, improved postural management and pain relief. Despite the temporary effect of injections, gains in motor function have been reported to last as long as 12 months.¹¹

Several studies have demonstrated the benefits of BoNT-A injections for ambulant CYPwCP in Gross Motor Function Classification System (GMFCS) levels I–III,¹² particularly at single level use (injection at one level; eg, the calf complex to treat equinus foot posture).^{3,15–17} A meta-analysis of double-blind, randomised controlled trials (RCTs) confirmed superiority of BoNT-A over placebo injections into the calf complex on improvement of gait in patients with spastic equinus.¹⁸ BoNT-A treatment, in combination with other rehabilitation treatments, has resulted in a significant improvement in functional goal attainment over and above those in a non-BoNT-A treatment group,¹⁹ with improvements in gait parameters, pain reduction and splint tolerance.^{20–25}

Nevertheless, despite positive outcomes for single level use, RCTs of the effectiveness of multilevel use of BoNT-A injections report mixed results.^{24,25} Although a recent systematic review of interventions for CYPwCP, identified BoNT-A treatment as one of few interventions

with a sound evidence base²⁰, a recent Cochrane Collaboration report by Blumetti *et al*²⁷ showed less favourable results. The report reviewed 31 studies, assessing 1508 participants and concluded that there is limited evidence to show that BoNT-A, when compared to placebo or usual care, improves walking, joint motion, satisfaction with outcome of treatment and muscle spasticity in CYPwCP. Sample sizes in BoNT-A studies are often small and predominately based on short-term outcome (3–6 months) with few assessing outcomes beyond 6 months.

Although it is widely acknowledged that BoNT-A treatment is not a 'stand-alone' treatment, detailed information regarding the adjunctive measures used in conjunction with BoNT-A is often lacking, making evaluation of its efficacy difficult.^{28–30} Some authors have highlighted the difficulty in relating changes in impairment measures following BoNT-A treatment to functional improvements in CYPwCP, with little reference made to minimal clinically important differences (MCIDs).²⁴ This raises concerns that current standardised outcome measures, focusing predominantly on impairment measures (without relating this to other domains of the ICF), may lack the sensitivity to pick up meaningful changes following injections, or indeed overestimate treatment effects if these do not relate to MCIDs, all highly pertinent when planning repeat treatment.^{24,27,31}

Recent studies investigating pathophysiological changes within hypertonic muscle have highlighted potential histological changes following both single and repeated BoNT-A treatment.³² A number of authors have suggested potential harm following repeated BoNT-A use.^{33–36} However, both positive and negative effects have been reported, and a variability in measurement techniques and muscles assessed makes comparison between studies challenging.^{37–42} Although BoNT-A has been described as a 'reversible treatment',⁴³ some authors suggest that BoNT-A exposure in CYPwCP may be associated with impaired muscle growth in the short-term^{44–47} and potential long-term atrophy.^{41,45,48}

The WHO's International Classification of Functioning, Disability and Health (ICF) encourages evaluation of adaptive skills (enabling activities and participation) and health-related quality of life (HRQoL) in order to target interventions that are meaningful to CYPwCP and their families (figure 1). However, evidence for BoNT-A treatment remains mostly related to measures of body functions and structures, and less evidence pertains to activity and participation.^{22,25,49–51} Few trials have explored improvement in the activity and participation domains or HRQoL after BoNT-A injections,^{24,52} and qualitative data relating to CYP and caregivers experience are rarely incorporated.^{53–55}

Longitudinal changes are not well characterised, and evidence of impact on CYPwCP is elusive. The uncertainty that exists around BoNT-A treatment has resulted in a call to extend the period that CYPwCP are followed up after BoNT-A treatment beyond the short-term, 12-week period,⁴⁴ with an imperative to evaluate interventions

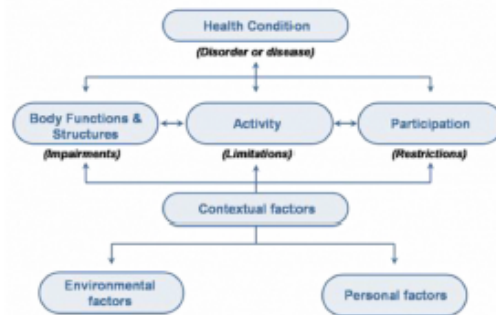


Figure 1 WHO's International Classification of Functioning, Disability and Health schematic representation of living with a health condition.

with BoNT-A using more sensitive outcome measures that evaluate meaningful aspects of health and quality of life for CYPwCP and families.^{45 44 56-58}

Concern has been raised that BoNT-A treatment may be overprescribed for CYPwCP^{55 56 58} if there is little guidance about which patients will benefit, risking potential harm if outcomes are unclear.^{58 59-61} While clinical evidence suggests that BoNT-A remains a valuable treatment option,^{15 58 62 63} there is a need to optimise its use by developing clear guidelines and robust treatment algorithms in order to predict which children and young people will benefit from the addition of BoNT-A intervention to their overall management programme and when it is preferable to consider other treatment options.

The Toxin Study

This paper describes the protocol for a pragmatic prospective longitudinal observational study in an established paediatric movement disorder service in London, UK. As BoNT-A treatment is considered best practice care for focal hypertonia management in CP,^{19 21 48} there are practical and ethical concerns regarding the inclusion of a 'no treatment' control group and so a comparator was deemed not ethically appropriate.

The aims of this study are to:

1. Investigate clinical and patient reported outcomes (of body structures and function, quality of movement, activities and participation and HRQoL) associated with lower limb BoNT-A injections in ambulatory CYPwCP over a 12-month period.
2. Determine any factors associated with a response to BoNT-A treatment.
3. Explore qualitatively how standardised clinical outcome measures relate to the experiences of CYPwCP following BoNT-A treatment.

METHODS

Study design

This is a mixed methods study comprising of two phases:

Phase 1: to meet objectives 1 and 2, we will use a prospective longitudinal study using a one-group repeated measures design with each child acting as their own control.

Phase 2: to meet objective 3, we will conduct interviews with a subgroup of CYPwCP and parent/carers from phase 1 to elicit their experiences and views of change following BoNT-A treatment.

Using a convergent mixed methods approach, quantitative data from phase 1 will be synthesised with qualitative data from phase 2 in order to gain understanding of the impacts of BoNT-A treatment.^{55 64}

Study sample and recruitment

Potential study participants will be identified from clinical lists of the Movement Disorder Service at Great Ormond Street Hospital for Children (GOSH). All eligible participants will be invited to take part in phase 1 and will be enrolled sequentially. A subgroup of CYPwCP and their parents/primary carers will then be invited to participate in phase 2 following review at 6 months postinjection. Purposive sampling will be used to ensure a representative sample of CYPwCP within each GMFCS level.

Inclusion and exclusion criteria

Participants with a confirmed diagnosis of CP meeting the following criteria will be included: (1) ambulant, functioning at GMFCS levels I-III; (2) aged between 4 and 18 years; and (3) prescribed lower limb BoNT-A injections in their clinical management plan for dynamic hypertonia limiting functional goals or causing pain.

Children will be excluded if they have previously had: (1) orthopaedic surgery to the injected muscle; (2) neurosurgery for tone reduction (selective dorsal rhizotomy); (3) lower limb BoNT-A injections in the last 6 months, or currently have (4) unrelated musculoskeletal problems such as recent acute injury or congenital structural abnormality; (5) no access to a block of therapy (defined as a minimum of 6 weekly sessions) postinjections; and (6) an inability to complete baseline assessments due to capacity, ability or willingness.

Parents: every effort will be made to support the inclusion of all families invited to participate in the study (including those where English is not their first language). We will use translators when required to ensure that there is sufficient understanding to complete the measures.

INTERVENTION

Motor assessment

An experienced multidisciplinary team (consisting of a consultant paediatrician/neurologist and senior physiotherapist) will identify muscle groups to be injected. Muscle selection will vary between participants according to the presence of dynamic hypertonia (based on clinical assessment with reference to standard definitions⁶⁵), related functional impairment and individual goals of the CYPwCP. All participants will receive a 6-week block

of therapy post injection from their local therapy team, delivered locally in the community as per usual care. Details of dosage including frequency, location and type of therapy (eg, goal directed therapy and strengthening) together with participation activities will be recorded including any additional intervention such as casting or change in orthotic provision. This will be required in order to describe the content and parameters of usual care in as much detail as possible.⁶⁶

Administration of BoNT-A

We will follow standard clinical practice prescription of BoNT-A at GOSH which involves administration of 500U Dysport (abobotulinumtoxinA, Dysport Ipsen Ltd) diluted in 1ml of normal saline, up to a maximum dose of 30 units/kg/body weight or a total dose up to a maximum of 1000 units per injection session. All CYPwCP will continue to receive BoNT-A injections under ultrasound guidance as a day case, either under sedation with local analgesia or under general anaesthetic. Adverse events will be recorded, and standard reporting of dose per muscle and follow-up will be as per current clinical policy.

Training and fidelity

Clinical staff collecting study data are experienced members of the tertiary service with extensive experience of working with CYPwCP (mean 21 years, range 13–33 years). A standardised protocol for measurement and documentation is used in the clinic, and an additional study manual with instructions for clinicians will be used to ensure consistency during the study. Two half-day training sessions will be provided for clinicians collecting study data prior to the start of recruitment. Monthly meetings with clinicians by the research team will ensure consistency and adherence to study protocol.

Staggered patient recruitment and data collection will commence in September 2017, and each participant will be followed up for a period of 12 months (figure 2). Data collection and final analysis of participant data are expected to be completed by September 2021. All decisions regarding clinical care, assessment frequency and BoNT-A injections will continue as per usual clinical practice. Standardised clinical assessments and outcome measures will be performed at four time points T_0 – T_3 . The timings and rationale for these are summarised in table 1.

All participants who have not undergone a surgical procedure will be assessed at T_3 , independent of outcome at T_2 . This will facilitate analysis of factors associated with changes in impairment, activity, participation and HRQoL following BoNT-A treatment and evaluate time to reinjection over 12 months. The need for reinjection will be determined by clinical examination (documentation of a technical response, eg, change in MTS), evaluation of goal (Canadian Occupational Performance Measure) scores and in consultation with families and local team as per usual clinical practice.

Validated outcome measures for all ICF domains

The standardised outcome measures used in the study are summarised within the ICF domains in figure 3 with administration details of the measures summarised in table 2. Outcome measures follow GOSH standard clinical practice with primary outcome measures marked in italics.* Patient assessment takes between 60 and 90 min.

Classification of the participants

Gross Motor Function Classification System – Expanded and Revised (GMFCS-E&R)

The GMFCS-E&R¹² is an internationally recognised five-level system to classify the motor abilities of CYPwCP aged 4–18 years, with level I CYPwCP being identified as the most physically able and level V as the least. It is valid and reliable and frequently used in both research and clinical practice. Only ambulant CYPwCP classified as GMFCS levels I–III will be included in this study.

Classification of CP

Participants are classified according to the distribution (unilateral or bilateral) and tone presentation (hypertonia will be identified as predominantly spastic, dystonic or mixed in type) as identified by the guidelines of the surveillance of cerebral palsy in Europe network (SCPE).⁶⁷

OUTCOME MEASURES

Primary outcome measures

Quality Function Measure (QFM) is an observational criterion referenced measure designed to evaluate the quality of movement in standing and walking skills in CYPwCP.⁶⁸ It is used in conjunction with the Gross Motor Function Measure (GMFM) using dimensions D and E, which focus on 'standing' and 'walking, jumping and running skills', which are considered proxy clinical gait measures. The GMFM is the 'gold standard' tool for evaluating gross motor function in CYPwCP, evaluating 'how much' of a gross motor skill a child can perform.⁶⁹ However, there are concerns regarding GMFM's sensitivity in capturing subtle yet meaningful change postintervention, due to 'ceiling effects' of the measure when used with ambulant CYPwCP in GMFCS levels I–III.^{22 68 70} The QFM scores movement quality and assesses 'how well' a child performs gross motor tasks.⁶⁸ It has shown excellent rater and test-retest reliability (Intraclass correlation (ICC) 0.89–0.97). Minimal detectable change estimates (6%–9%) suggest that the scale has potential as an evaluative measure (V Wright, personal communication, 8 May 2018). However, to date, there are no published studies evaluating the responsiveness of QFM following BoNT-A injections.

In order to minimise bias, the video analyst will be blinded to the stage of treatment and assessment time point (ie, pre T_0 or post T_{1-3} injection). To conceal these time points, each video containing GMFM D and E (standing and walking) dimensions is anonymised and randomly allocated a letter by a coworker not involved in the service. To minimise recall bias, a time lag will be

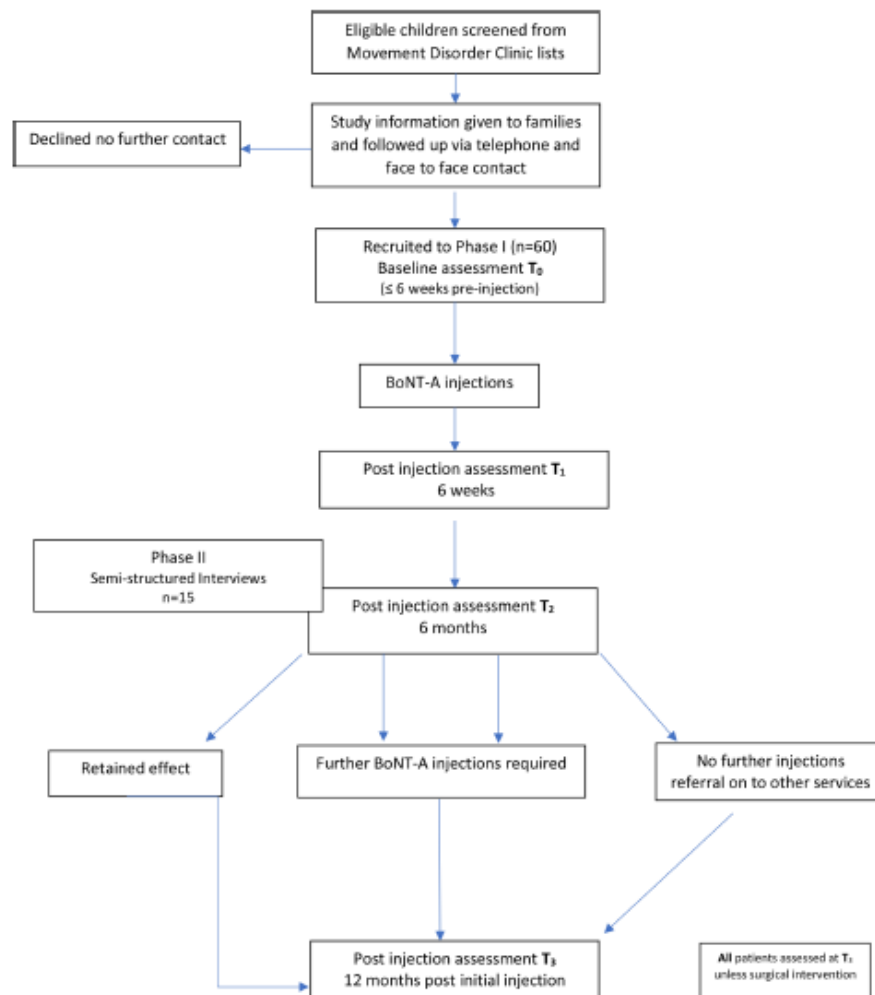


Figure 2 Study design flow chart of patient recruitment and data collection during the study. BoNT-A, Botulinum neurotoxin-A.

built in of 2 weeks and videos of at least 10 other children will be scored before scoring the video of the same child at a different assessment time point. This is in keeping with previous QFM reliability studies that suggest a gap of 2 weeks before evaluating test–retest scores.^{68–70} Data will be entered into a secure database without access to previous scores until scoring for all assessment time points is complete.

COPM is a goal attainment tool modified for use in the paediatric population and frequently used in neuro-disability research.^{71–75} It identifies concerns regarding ‘occupational performance issues’, that is, the ability to carry out functional tasks, allowing the identification of goals and has been used to document change post BoNT-A rehabilitation.⁷⁴ In the paediatric population,

areas of concern in a child’s self-care, activity and leisure are explored during the preassessment appointment with the clinical team. *COPM* has demonstrated high retest reliability (ICC 0.76–0.89), sensitivity to change and good content, construct and criterion validity for CYPwCP receiving BoNT-A.^{75–76} Families are asked to identify up to three areas of concern that they and their child hope to improve following lower limb BoNT-A injections. Whenever possible, goals are set with the child’s input.⁷⁷ The child and parents are asked to rate their perception of both current performance and their satisfaction with this performance on a 1–10 ordinal scale. A score change of two or more points is considered clinically significant.^{72–78}



Table 1 Timings of study assessments T₀-T₃

T ₀	Preinjection baseline measures	1-6 weeks before injection
T ₁	6 weeks postinjection	Estimated time to reach target threshold for BoNT-A. 'Evaluation of efficacy of injections'.
T ₂	6 months following injection	Expected completion of pharmacological action. 'Evaluation of retention of effects post injection'.
<p>At T₂, as per usual clinical practice, there are three possible outcomes for participants:</p> <ul style="list-style-type: none"> ▶ Favourable response to injections with retention of effects – no further injections indicated at this time. ▶ Favourable response to injections – listed for a second injection cycle. ▶ Non favourable response to injections – discharged to other services (eg, neurosurgery/orthopaedics). 		
T ₃	12 months following initial injection	End of study

Secondary outcome measures

Modified Tardieu Scale (MTS) is a recognised clinical measure to differentiate dynamic spasticity from fixed contracture in a muscle. It determines the passive range of movement at two different movement velocities fast (R1) measuring dynamic muscle length and slow (R2) measuring static muscle length, with the relative difference between the two (R2-R1) determining the dynamic tone component of the muscle contracture.^{79,80} It is measured in degrees with a universal goniometer using standardised testing positions for each muscle. It has been postulated that the larger the dynamic tone component, the more amenable it is to treatment with BoNT-A.⁷⁸ It is more effective than

the Modified Ashworth Scale in identifying the presence of spasticity (88.9%, kappa=0.73, p=0.000) and the presence of contracture (77.8%, kappa=0.503, p=008).

Faces Pain Scale is a self-report measure of pain intensity developed for children, which has been shown to have good psychometric properties for pain reporting (modified for use by carer when the child is unable to self-report). The scale shows a close linear relationship with visual analogue scales. It is measured by an ordinal scale from 0 to 10 with pictorial representation of faces. A change score of 2 or more is said to be clinically significant.⁸¹

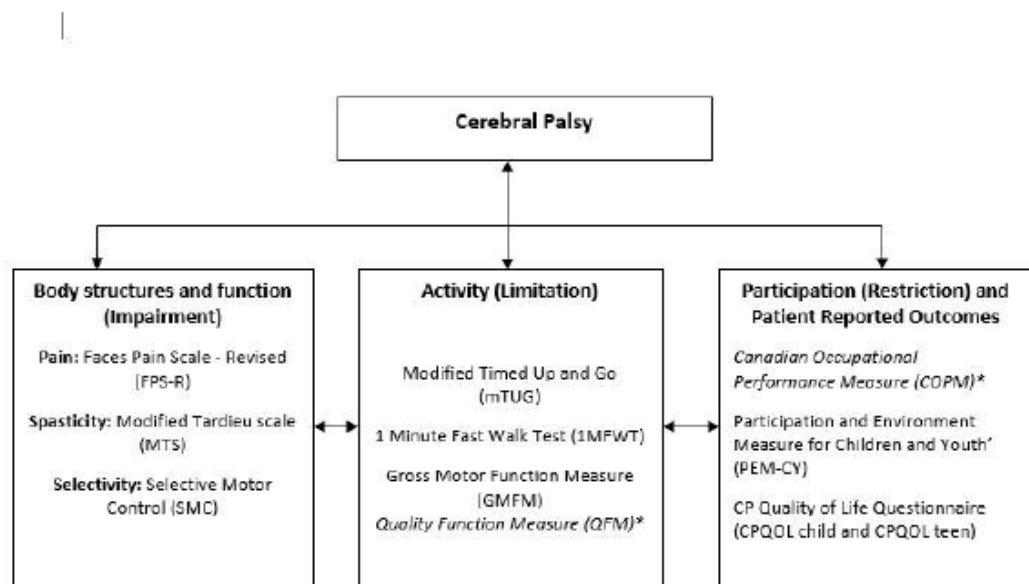


Figure 3 Schematic representation of ICF domains including standardised outcome measures used in the study. ICF, International Classification of Functioning, Disability and Health.

Table 2 Summary of outcome measures used in the study

ICF domains	Assessment	Outcome measures	Method of administration	Units	Description
Body functions and structures (impairment)	Hypertonia and dynamic range of movement	Modified Tardieu Scale (MTS)	Standardised goniometry placement	Degrees	MTS measured at injected muscles. The difference between the slow stretch R2 and a fast stretch R1 is reported as the 'dynamic range' and when a difference is present, this 'dynamic range' is reported to be amenable to treatment with BoNT-A.
	Pain	Faces Pain Scale (FPS-R)	Score assigned by CYPwCP	Score 0-10	FPS-R has been shown to have good psychometric properties for pain reporting (modified for use by carer when CYPwCP unable to self-report)
	Selective motor control	Selective Motor Control scale (SMC)	Score assigned by clinician	Score 0-4	SMC of the ankle is assessed using a standardised test procedure.
Activity (functional limitation)	Gross motor function	Gross Motor Function Measure (GMFM) D&E walk/run/jump dimensions)	Video recorded Standardised assessment form Scored by clinician	% score	The GMFM is designed to evaluate change in gross motor function over time in CYPwCP. GMFM is considered the standard outcome assessment tool for clinical intervention in CP, dimensions D&E will be used and are considered a Proxy Functional Gait Measure. Families are consented for video storage in accordance with the Great Ormond Street Hospital policy.
	Quality of Gross Motor Function	Quality Function Measure (QFM)	video scored later by Principal Investigator (LRK) blinded to treatment stage	% score for five quality attributes	The QFM is an observational validated measure that captures the quality of movement of the items in the GMFM (D&E dimensions) This is scored from GMFM video involving no extra assessment time for CYPwCP.
	Balance/functional mobility	Modified Timed up and Go Test (mTUG)	Timed standardised test (from sitting CYP stands and walks distance 3 m touches star returns to seat)	Seconds	mTUG integrates transitions and walking skills and provides a meaningful measure of capability. It has been shown to be a reliable outcome measure for assessing functional mobility in CYPwCP. Proxy Functional Gait Measure.
	Walking ability (Efficiency)	1 min fast walk test (1MFWT)	Distance recorded (5 min rest followed by walking for 1 min in a 9 m corridor at maximum walking speed without running. CYPwCP permitted to use normal walking aids and orthoses).	Metres	1MFWT is a good discriminator of functional ability for dynamic balance, muscle performance and endurance. Proxy Functional Gait Measure

Continued



Table 2 Continued

ICF domains	Assessment	Outcome measures	Method of administration	Units	Description
Participation (restriction)	Involvement in daily activities	Participation and Environment Measure for Children and Youth (PEM-CY)	Parent-reported questionnaire (25 item -25 min to complete) Answered at home or in clinic	Summary score	The PEM-CY assesses participation frequency and involvement in home school and community, along with environmental factors within these settings. Can be completed online at home or in clinic on a handheld device/paper format while waiting for the child's assessment to be completed.
Healthrelated quality of life	Quality of life across seven domains	Cerebral Palsy Quality of life measure (CPQOL)	CYP (or proxy) reported questionnaire CPQOL-Child/CPQOL-Teen Answered at home or in clinic	Mean Domain Score	The CPQOL-Child is designed to assess condition-specific quality of life of children across seven domains for children aged 4–12 years – parent report for children aged 4–12 years and a self-report for children aged 9–12 years (52–66 items). CPQOL-Teen 13–18 years. Adolescent self-report version and a parent version (72–89 items).
Goal setting (ICF domains)	Selection of goals CYP hope to improve following	Modified Canadian Occupational Performance Measure (mCOPM)	In clinic three goals set by CYP and family preinjection Scores assigned postinjection	Score (1–10)	mCOPM rates perception and satisfaction of CYP's performance on a 1–10 ordinal scale. A score change of >2 points is considered clinically significant.

BoNT-A, botulinum toxin-A; CYPwCP, children and young people with cerebral palsy; ICF, International Classification of Functioning, Disability and Health.

Selective Motor Control is a good discriminator of selective motor control and assesses a child's ability to voluntarily and selectively control the dorsiflexors of the ankle.⁷⁷ It is measured by an ordinal scale between 0 and 4. Higher score indicates better selectivity, inter-rater agreement has been shown to be moderate to good (kappa=0.58–0.77) with strong test–retest reliability (kappa=0.88–1).^{79, 82}

One Minute Fast Walk Test has been chosen as a proxy gait measure and is a good discriminator of functional ability for dynamic balance, muscle performance and endurance.⁸⁵ Participants walk for 1 min along a 9 m corridor at maximum speed without running. They are able to use their usual walking aids and orthoses. Distance is calculated to the nearest 10 cm. It shows concurrent validity with the GMFM, with significant correlation between GMFM score and distance walked ($r=0.92$) and good reliability (ICC: 0.97).⁸⁴

Modified Timed Up and Go is a good discriminator of balance, anticipatory postural control and functional mobility in CYPwCP. Participants are timed rising from a chair, walking 3 m to touch a star on the wall and returning to sit down as quickly as they can without running. Participants are able to use their usual walking aids and orthoses. The measure differentiates performance between CYPwCP at GMFCS levels I–III. It has shown excellent inter-rater reliability (ICC 0.83–0.99).⁸⁵

Participation Environment Measure – Child and Youth (PEM-CY) is an innovative parent-reported participation measure for use with CYP between 4 and 18 years. It measures CYPwCP's participation at home (10 items), school (5 items) and community (10 items), taking into account the environmental challenges within each setting. Summary scores for participation frequency, child's involvement and parental desire for change are calculated for all domains. PEM-CY has demonstrated good internal consistency (ICC 0.72–0.83) and test–retest reliability (ICC 0.76–0.89).⁸⁰

Cerebral Palsy Quality of Life Measure (CPQOL) is an HRQoL assessment administered by questionnaire, specifically designed for CYPwCP. It quantifies 'well-being' across seven key HRQoL domains. Items are scored on a nine-point rating scale, then summed and averaged to generate seven domain scores. There are two child-reported (CPQOL-Child: 9–12 years and CPQOL-Teen: 13–18 years) and two proxy-reported versions dependent on child's age and cognitive ability (CPQOL-Child Primary caregiver: 4–12 years and CPQOL-Teen Primary care giver: 13–18 years). The questionnaire designers have stipulated a minimum age of 9 years for child self-reporting, however significant disagreement has been reported between child and parent proxy reports in many HRQoL instruments, and the child's perspective will be sought whenever possible in this study.⁸⁷ The CPQOL has demonstrated good internal consistency (child ICC 0.74–0.92; teen 0.81–0.96) and adequate test–retest reliability (child ICC 0.76–0.89; teen 0.59–0.83).^{88, 89}

Semistructured interviews

Interviews will be used to elicit CYPwCP and parent/carers views of change following BoNT-A treatment. These are expected to last 60 min for parents and up to 30 min for children and will take place at home or in the hospital (depending on family preference). Interviews will be guided by a predetermined interview schedule, which will explore perceived change across all ICF domains to facilitate comparison with quantitative outcome measures, as well as investigate the acceptability of the standardised outcome measures used in phase 1 of the study. Parents will be interviewed separately from CYPwCP, although individual preference for parents to be present or absent during interviews with their child will be respected. Interviews with CYPwCP will be tailored to their age, cognitive and communication ability using a variety of different techniques, including art-based activities. Offering a toolkit of different creative techniques will ensure that the activities will be accessible to all CYPwCP involved in the interviews, acknowledging their different skills and personalities and their cognitive and physical abilities that is particularly important in this population of CYP.⁹⁰ To ensure a representative sample of participants for phase 2, CYPwCP with a good, moderate and poor response to toxin (determined by the clinical team at the 6-month assessment) within each GMFCS level (I–III) will be invited to take part in phase 2. All interviews will be audio recorded with permission from participants.

Sample size

Phase 1: this study has been powered to detect a difference on one of the two primary outcome measures, the COPM. The sample size power calculation is based on anticipated change in the COPM goal performance at the primary end point T1 (6 weeks postintervention) after BoNT-A treatment. A change in score of 2 or more points on the performance scale of the COPM would be considered clinically meaningful.^{72–78} An earlier study of lower limb BoNT-A intramuscular injections yielded SD between 1.4 and 1.7 for COPM performance.⁷⁷ Based on a conservative estimate using a mean change of two points on the COPM performance scale (power 0.8, two tailed, $p < 0.05$), 36 participants (12 in each GMFCS level) are required. Allowing for attrition and missing data over a 12-month period, a total of 60 participants (20 in each GMFCS level) will be recruited for phase 1 of the study.

As there are no studies reporting Quality Function Measure (QFM)⁶⁸ as a primary outcome measure following BoNT-A injections, no data exist to inform a power calculation. It is anticipated that the results from this study will provide power calculation data for use in future multicentre trials using QFM.

Phase 2: a sample size of approximately 15 CYPwCP (five from each of the GMFCS levels I–III) and their parent/carer is anticipated to be sufficient to reach thematic saturation for the qualitative element of the study.⁹¹

Data analysis

Descriptive analysis of the prospective study will provide information on baseline characteristics of impairment, activity, participation and HRQoL. Means and SD will be used for normally distributed data and medians and IQRs for skewed data. Other demographic data will be described in a similar way with frequencies and proportions used for categorical information. The primary outcomes of the intervention will be assessed using generalised estimating equations for longitudinal analysis to evaluate differences in continuous data at postintervention time points. Multilevel regression models will be used to investigate the importance of the various potential predictors over a 12-month period on the four main outcomes: impairment, activity, participation and HRQoL. First, univariate relationships will be explored, and then if appropriate, we will fit a multivariable model for each outcome.

All interviews will be transcribed verbatim, and transcripts will be checked by the interviewer. Qualitative data will be analysed using Braun and Clarke's six phase framework for thematic analysis figure 4.⁹² Two researchers (LRK and KO) will undertake analysis of the transcripts to determine consistent themes and will then map these onto results from standardised outcomes. This will allow themes to emerge that can then be used to evaluate how closely standardised outcome measures relate to family experience.

Participant and data management

Electronic data will be managed through a secure database held in GOSH. Participants will be allocated an identification code that will be used to deidentify their files and forms. Pseudonyms will be used in all reports and publications, and direct quotations will be anonymised. Paper documents and other manual files will be appropriately filed and stored securely in a locked filing cabinet at GOSH. Demographic information and consent forms will be stored separately to research data. Classification measures, child demographics and related information will be taken prior to baseline for the purposes of stratification and description of the sample. Audio and visual recordings will be uploaded onto secure password-protected encrypted National Health Service computers and deleted from the recording device immediately after uploading. This protocol has been reviewed and approved by the Research and Development team and Caldecott Guardian at GOSH.

Patient and public involvement

Children and young people with CP and their parents have been involved in the development of this project, exploring the importance of the research, the appropriateness of the research questions, the acceptability of the research methods and best methods for disseminating findings. Fifteen ambulant CYPwCP receiving BoNT-A treatment at GOSH and their parents were consulted individually. A wider population of CYPwCP and their parents were also consulted via the SCOPE website and



Figure 4 Braun and Clarke's six-step approach to thematic analysis.

the advisory groups for CYPwCP at Brunel University and Young People's Advisory Group at GOSH.

Reference group/steering group

Three parents (all mothers) and three CYPwCP (two boys and one girl (not participants)) continue advising on the study through membership of the study steering group

(parents) or reference group (CYP). Three professionals (two physiotherapists and one doctor) are also part of the steering group. By including CYPwCP and families perspectives together with regular contributions from practising clinicians within the service, we hope to ensure the inclusion of important values and preferences from families and clinicians alike, ensuring that the findings of the study remain relevant and applicable to the management of ambulant CYPwCP.^{24 95 94}

DISCUSSION

This paper presents the protocol for a novel pragmatic prospective longitudinal observational study of BoNT-A use in ambulant CYPwCP at an established tertiary children's centre in the UK. It will measure outcomes across all domains of the ICF and HRQoL over a 12-month period to observe change and examine factors associated with positive or negative response to lower limb BoNT-A injections. The introduction of a standardised outcome measure, QFM, to evaluate any change in movement quality following BoNT-A treatment will further inform exploration of the relationship between tone reduction and changes in activity, as well as any influence on participation and HRQoL for our cohort of CYPwCP. Mixed methods research designs are considered by many to be essential in the study of therapeutic interventions in CP.²⁵ Including qualitative study data will ensure that the experiences of CYPwCP following BoNT-A injections are elucidated, considered and further understood.

This study, by identifying patterns of response to BoNT-A injections in key aspects of health across all the ICF domains, will provide clinicians and families with meaningful information to inform future treatment planning and optimise the use of BoNT-A in CYPwCP. Evidence will be generated about the appropriateness of the outcome measures used in detecting meaningful change after BoNT-A injections as well as their acceptability to CYP. In addition, the relationship between the standardised outcome measures used to capture treatment effect and the perception of outcome by children and their families will be investigated.

The results of this study will assist in the development of a pragmatic set of standardised clinical outcome measures (recognising minimum clinically important differences) in order to evaluate the effects of BoNT-A treatment in this cohort of patients. We hope this work will inform future evaluative research; working towards closer consensus on patient selection, injection frequency and consideration of how long treatment should continue, in order to assess the value of long-term use of BoNT-A treatment and its role in the management of CYPwCP.

A dissemination strategy has been devised to ensure the findings of this research are made widely accessible to families and professionals in order to maximise impact on the care of CYPwCP. Working in partnership with parent groups will strengthen our dissemination strategy, ensuring findings are shared in a variety of accessible formats reaching

a wide range of families, professionals, as well as academics and policy makers helping ensure the findings are translated into practice. We will disseminate the results of the study through international peer-reviewed journals and at national and international conferences. A social media strategy will also be developed to ensure dissemination of a plain language summary of findings.

Author affiliations

¹Neuroscience Unit, The Wolfson Neurodisability Movement Disorder Service, Great Ormond Street Hospital For Children, London, UK
²Physiotherapy, UCL Great Ormond Street Institute of Child Health, London, UK
³Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), Great Ormond Street Hospital for Children, London, UK
⁴Peninsula Childhood Disability Research Unit (PenCRU), University of Exeter Medical School, University of Exeter, Exeter, UK

Twitter Lesley R Katchburian @KatchLesley and Eleanor Main @MainEleanor

Acknowledgements We would like to thank the clinical team at The Wolfson Neurodisability Movement Disorder Service at Great Ormond Street Hospital for Children (GOSH), especially, Dr Belinda Crowe, Xanthe Hodgson, Josephine Sotri, Emilie Hupin, Katharine Philipps, Tessa Burnett, Sarah Foster, Agnieszka Rozborska and Stephanie Cawker. We would also like to thank Dr Jo Wray from the Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID) at GOSH for support and advice on the planned data analysis. Many thanks to Professor Roslyn Boyd, Scientific Director of the Queensland Cerebral Palsy and Rehabilitation Research Centre for her valuable suggestions regarding methodology and selection of outcome measures and Dr Margaret Mayston (UCL) for her early contribution to the preliminary study design. Most importantly, huge thanks to all the children and their families who have been involved in the development of the research idea, provided advice and input to the study protocol and those who have agreed to participate in the study.

Collaborators Belinda Crowe; Xanthe Hodgson.

Contributors All authors conceived and designed the study. LRK developed the protocol with input from all authors. LRK and LC are responsible for recruiting and supporting all the participants. LRK, EM and KO will conduct the data analyses. LRK and LC wrote the first draft of the manuscript; all authors reviewed this and have approved the final manuscript.

Funding Lesley Katchburian is funded by a National Institute for Health Research (NIHR) Clinical Doctoral Research Fellowship Award (ICA-CDRF-2015-01-037). The study is also supported by the NIHR GOSH BRC at UCL GOSH Institute of Child Health. Kate Oulton is an NIHR Senior Nurse and Midwife Research Leader.

Disclaimer The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Lesley R Katchburian <http://orcid.org/0000-0002-7523-7083>
 Eleanor Main <http://orcid.org/0000-0002-9739-3167>
 Christopher Morris <http://orcid.org/0000-0002-9916-507X>
 Lucinda J Carr <http://orcid.org/0000-0001-9238-108X>

REFERENCES

- 1 Odding E, Roebroek ME, Stam HJ. The epidemiology of cerebral palsy: Incidence, Impairments and risk factors. *Disabil Rehabil* 2006;28:183-91.
- 2 Molenaers G, Van Camperhout A, Fagard K, et al. The use of botulinum toxin A in children with cerebral palsy, with a focus on the lower limb. *J Child Orthop* 2010;4:183-95.
- 3 Koman LA, Mooney JF, Smith BP, et al. Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial. *J Pediatr Orthop* 1994;14:299-303.
- 4 Koman LA, Paterson Smith B, Balkrishnan R. Spasticity associated with cerebral palsy in children: guidelines for the use of botulinum a toxin. *Paediatr Drugs* 2003;5:11-23.
- 5 Ward AB, Molenaers G, Colosimo C, et al. Clinical value of botulinum toxin in neurological indications. *Eur J Neurol* 2006;13(Suppl 4):20-6.
- 6 Tedroff K, Granath F, Forssberg H, et al. Long-Term effects of botulinum toxin A in children with cerebral palsy. *Dev Med Child Neurol* 2009;51:120-7.
- 7 Hoare BJ, Imms C. Upper-Limb injections of botulinum toxin-A in children with cerebral palsy: a critical review of the literature and clinical implications for occupational therapists. *Am J Occup Ther* 2004;58:389-97.
- 8 Lukban MB, Rosales RL, Dressler D. Effectiveness of botulinum toxin A for upper and lower limb spasticity in children with cerebral palsy: a summary of evidence. *J Neural Transm* 2009;116:319-31.
- 9 Ryll U, Bastiaenen C, De Ble R, et al. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review. *Dev Med Child Neurol* 2011;53:210-6.
- 10 Aoki KR, Ranoux D, Wissel J. Using translational medicine to understand clinical differences between botulinum toxin formulations. *Eur J Neurol* 2006;13(Suppl 4):10-19.
- 11 Ellega de Souza M, Renata Calhes Franco MFMS, Fabiano Politti CSO. Effect of botulinum toxin A on spasticity and function in children with cerebral palsy: a systematic review. *Med Sci Tech* 2014;55:11-15.
- 12 Pallsano R, Rosenbaum P, Waiter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
- 13 Desloovere K, Molenaers G, Jonkers I, et al. A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. *Eur J Neurol* 2001;8(Suppl 5):75-87.
- 14 Gough M, Fairhurst C, Shortland AP. Botulinum toxin and cerebral palsy: time for reflection? *Dev Med Child Neurol* 2005;47:709-12.
- 15 Svehlik M, Kraus T, Steinhwender G. Repeated multilevel botulinum toxin a treatment maintains long-term walking ability in children with cerebral palsy. *Ceska a Slovenska Neurologie a Neurochirurgie* 2012;75:737-41.
- 16 Delgado MR. The use of botulinum toxin type A in children with cerebral palsy: a retrospective study. *Eur J Neurol* 1999;6:s11-18.
- 17 Delgado M, Tilton A, Gormley M. AbobotulinumtoxinA injection in muscles outside the gastrocnemius-soleus complex in pediatric patients with lower limb spasticity. *Dev Med Child Neurol* 2017;59:80-1.
- 18 Cardoso ES, Rodrigues BM, Barroso M, et al. Botulinum toxin type A for the treatment of the spastic equinus foot in cerebral palsy. *Pediatr Neurol* 2006;34:106-9.
- 19 Wallen M, O'Flaherty SJ, Waugh M-CA. Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial. *Arch Phys Med Rehabil* 2007;88:1-10.
- 20 Helnen F, Desloovere K, Schroeder AS, et al. The updated European consensus 2009 on the use of botulinum toxin for children with cerebral palsy. *Eur J Paediatr Neurol* 2010;14:45-66.
- 21 Fehlings D, Novak I, Berweck S, et al. Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement. *Eur J Neurol* 2010;17(Suppl 2):38-56.
- 22 Love SC, Novak I, Kantish M, et al. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. *Eur J Neurol* 2010;17(Suppl 2):9-37.
- 23 Metaxiotis D, Siebel A, Doederlein L. Repeated botulinum toxin A injections in the treatment of spastic equinus foot. *Clin Orthop Relat Res* 2002;394:177-85.
- 24 Wright FV, Rosenbaum PL, Goldsmith CH, et al. How do changes in body functions and structures, activity, and participation relate in children with cerebral palsy? *Dev Med Child Neurol* 2008;50:283-9.

Use of the Quality Function Measure (QFM) to evaluate changes in quality of movement in ambulant children with cerebral palsy following lower limb Botulinum Toxin A injections

Katchburian, L^{1,2,3}; Hodgson X¹; Hupin E¹; Phillips, K¹; Scerri J¹.

1. Motor disorders Service, The Wolfson Neurodisability Service, Great Ormond Street Hospital for Children (GOSH), London UK
 2. Centre for Outcomes and Experiences Research in Children's Health, Illness and Disability (ORCHID), GOSH, London, UK.
 3. University College London Great Ormond Street Institute of Child Health, London UK

Background

Quality of movement (QOM) is an essential component of effective motor skills in children with Cerebral Palsy (CP), influencing not only a child's functional activity level but also their participation opportunities. **Botulinum Toxin A (BoNT-A)** is an established treatment modality in the management of increased tone in CP and is frequently used in an attempt to optimize a child's functional skills and improve QOM. However, evidence associating reduction in dynamic spasticity and improvement in QOM is lacking and there is a demand for more sensitive outcome measures to evaluate the efficacy of BoNT-A use in CP. **Quality Function Measure (QFM)** is a standardised outcome measure evaluating QOM of standing, walking, jumping and running skills in ambulant children with CP. It is based on Dimensions D and E of the 'gold standard' Gross Motor Function Measure (GMFM) and is reported to be sensitive to change when evaluating therapeutic interventions and assesses movement quality in 5 dimensions: **Alignment, Stability, Coordination, Dissociation & Weightshift**

Objectives

To evaluate the feasibility of introducing the **Quality Function Measure (QFM)** into an established clinical setting to assess short term change in QOM following lower limb BoNT-A use in ambulant CP.

Methods

- This feasibility study forms part of a prospective longitudinal study evaluating the use of lower limb BoNT-A over a 12 month period
- 55 children with CP (29 Female, 26 Male) attending the BoNT-A clinic of a tertiary Motor Disorders Service were recruited.
- All children were ambulant classified as Gross Motor Function Classification System (GMFCS) levels I-III
- GMFCS levels: I n= 20 II n= 21 III n= 14



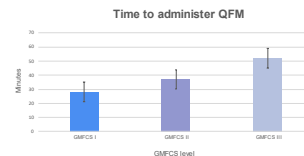
- Age at recruitment: Mean (SD) 7.4 years (2.8)
- Specialist Physiotherapists (≥15 years paediatric experience) administered the Gross Motor Function Measure (GMFM) pre injection and 6 weeks post injection following a standardized protocol (up to 3 trials) to digitally capture performance from frontal and coronal planes of movement as per QFM protocol



Examples of QFM items

Results

- Mean time to administer the test was 39 mins (range 26-60 mins).
- Administration time differed between GMFCS levels;
 - I = 28 mins (SD 2.4 mins)
 - II = 37 mins (SD 6.8 mins)
 - III = 52 mins (SD 8 mins)



- Level III children completed fewer test items but took longer to complete the tests and exhibited increasing fatigue.

Conclusions

- Introduction of QFM has proved acceptable in an established clinical setting provided clinic times are extended to incorporate the test
- QFM administration in the clinical setting (39 mins) compares to other standardised tests requiring post clinic evaluation
- Preliminary results suggest that improvement in QOM is associated with short term reduction in dynamic spasticity following BoNT-A
- However with a mean QFM scoring time of 60 minutes an important consideration is whether the lengthy scoring time for post clinic analysis prohibits its use in a clinical setting

References

- Living, K., Thores, K., Hegland, Y. & Gudermatz, E. M. 2017. Effects of Botulinum Toxin A and Goal Directed Physiotherapy in Children with Cerebral Palsy GMFCS Levels I & II. *Physical & Occupational Therapy in Pediatrics* 37, 268-282.
- Weigt, F., Rosenbaum, P., Fintels, D., Mostrom, R., Bruer, U. and Kim, M. (2014). The Quality Function Measure: reliability and discriminant validity of a new measure of quality of gross motor movement in ambulatory children with cerebral palsy. *Developmental Medicine & Child Neurology* 56(8), pp 770-778.
- Russell, D., Rosenbaum, P., Cadman, T., Gowland, C., Hardy, S., Jarvis, S. (1989). The Gross Motor Function Measure: A means to evaluate the effects of Physiotherapy. *Developmental Medicine & Child Neurology* 31, pp 341-352.
- Delaney, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E. and Galappi, B. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology* 39(4), pp 214-223. <https://pubmed.ncbi.nlm.nih.gov/9252663/>
- Tustin, K., Grew, H., Marlow, E. and Marlow, J. (2016). Inter-rater reliability and scoring duration of the Quality Function Measure in ambulant children with hyperkinetic movement disorder. *Developmental Medicine & Child Neurology* 58, 822-828. doi:10.1111/dmcn.13006



Lesley.katchburian@gosh.nhs.uk



AusACPDM/IAACD2022
1-5 March 2022 | Melbourne Australia
BETTER TOGETHER



AusACPDM/IAACD2022
1-5 March 2022 | Melbourne Australia
BETTER TOGETHER



The effects of lower limb Botulinum neurotoxin-A injections on goal-directed outcomes in ambulant children with cerebral palsy

Introduction

Botulinum neurotoxin type-A (BoNT-A) injections are commonly used in the management of hypertonia in children and young people with cerebral palsy (CYPwCP). There is limited evidence regarding their effect on goal-directed outcomes measures.

Meaningful child- and family-centred goal identification is an essential element of rehabilitation to ensure that any intervention provided is targeted towards the areas of their lives that are most important to CYPwCP. This prospective single-site study assessed goal attainment in ambulant CYPwCP undergoing BoNT-A injections using the Canadian Occupational Performance Measure (COPM).

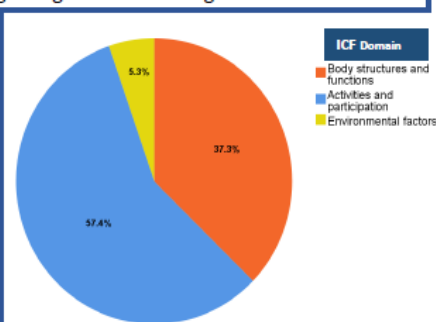


Figure 1: Breakdown of goals by ICF domain

Methods

Data were collected from 64 ambulant CYPwCP (Gross Motor Function Classification System levels I-III) aged 4 to 16 years undergoing lower limb BoNT-A injections at an established children's hospital in London, United Kingdom (UK). Changes in COPM scores were analysed at six weeks and six months post-intervention using Friedman tests. Participants' goals were classified according to the International Classification of Functioning, Disability and Health domains of body structures and functions, activities and participation, and environmental factors.

Results

COPM performance scores improved significantly from baseline to six weeks post-intervention (median difference 2; p-value <0.001) and from baseline to six months post-intervention (median difference 2; p-value <0.001). COPM satisfaction scores showed a similar pattern.

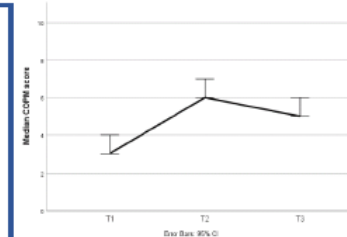


Figure 2: Median COPM performance scores over time

Of the 169 individual goals selected, 57.4% related to activities and participation, 37.3% related to body structures and functions and 5.3% related to environmental factors. Activities and participation goals displayed the most sustained positive responses to BoNT-A injections over time.

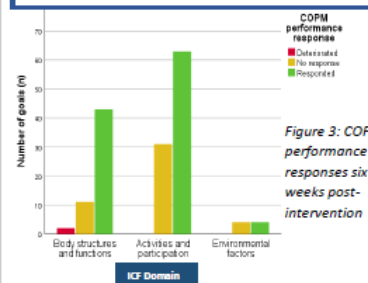


Figure 3: COPM performance responses six weeks post-intervention

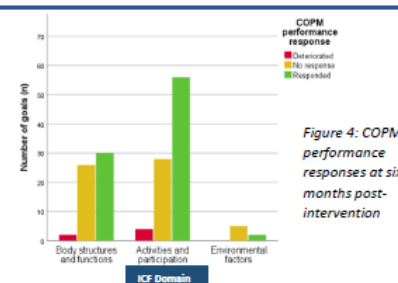


Figure 4: COPM performance responses at six months post-intervention

Conclusions

Lower limb BoNT-A injections in ambulant CYPwCP were associated with an improvement in COPM scores at both six weeks and six months following a single injection cycle. Further studies are required to evaluate COPM scores over a longer period and investigate how COPM scores may relate to other standardised outcome measures. A more detailed investigation of the responsiveness of goals throughout the domains of the ICF is also warranted to help improve the accuracy of predicting response to BoNT-A injections.

Katchburian, L.R.^{1,2,3}, Fielding, N.², Hodgson, X.¹, Carr, L.J.¹, Crowe, B.¹, Oulton, K.³, Morris, C.⁴, Wray, J.³, Main, E.²



AusACPDM/IAACD2022
1-5 March 2022 | Melbourne Australia
BETTER TOGETHER



Use of the Modified Tardieu Scale in the assessment of dynamic spasticity in children with ambulant cerebral palsy

Katchburian L^{1,2,3}, Kleiner A², Crowe B¹, Hodgson X¹, Carr L¹, Main E

¹Neurosciences Unit, The Wolfson Neurodisability Movement Disorder Service, Great Ormond Street Hospital for Children, London, UK ²Physiotherapy, UCL Great Ormond Street Institute of Child Health, London, UK. ³ORCID, Centre for Outcomes and Experience research in Children's Health Illness and Disability, Great Ormond Street Hospital for Children, London, UK

Introduction

Botulinum Toxin-A (BoNT-A) is an accepted treatment modality for the management of hypertonia in children and young people with cerebral palsy (CYPwCP). Increased tone (Hypertonia) is considered one of the primary motor impairments in CYPwCP and a significant contributor to secondary musculoskeletal impairments impacting on activity and participation.

The Modified Tardieu Scale (MTS) is an accepted clinical tool used to assess dynamic spasticity in CYPwCP (Figure 1), and is frequently used as part of the decision-making process to select treatment options for tone management.

It is performed by assessing

- Passive range of motion with low velocity (R2)
- Passive range of motion with high velocity 'dynamic catch' (R1)
- Dynamic component (R2-R1)

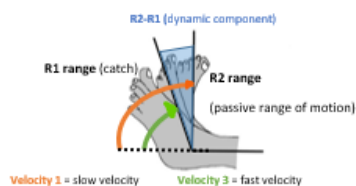


Figure 1 - Assessment of the muscle reaction of the MTS, consisting of the variables R1, R2 and the dynamic component R2-R1.

It has been postulated that the greater the dynamic component of muscle spasticity, the more amenable it is to treatment with BoNT-A¹.

Purpose of the study

In this prospective single site pragmatic study, the MTS was evaluated regarding its ability to predict medium term response to BoNT-A treatment in CYPwCP.



AusACPDM/IAACD2022
1-5 March 2022 | Melbourne Australia
BETTER TOGETHER



Methods

64 ambulant CYPwCP, (GMFCS Levels I-III) received lower limb BoNT-A injections for dynamic hypertonia. Dynamic spasticity was assessed with the MTS before (T₀), 6 weeks (T₁), and 6 months (T₂) after BoNT-A treatment.

Each treated muscle was categorised as responder or non-responder, based on the change in R1 between T₀ and T₂ with reference to reported Minimum Clinical Important Differences (MCIDs)².

Predictive factors and the predictive value of the MTS were investigated with statistical tests and a binominal regression model.

Results

The dynamic component in hamstring muscles (R2-R1) was found to be significantly different between responders and non responders at T₀ p=0.038

MTS variables at T ₀	Responder (n=17) median	Non-responder (n=22) median	p-value
R2	50.00	60.00	0.502
R1	85.00	85.00	0.288
R2-R1	25.00	20.00	0.038*

Table 1. Comparison of MTS variables between responders and non-responders of hamstrings muscles at T₀

Dynamic component (R2-R1) at baseline was predictive for response to BoNT-A in the hamstring muscles (p=0.024) with an odds ratio of 1.08.

Variables at T ₀	p-value	Odds ratio	95% C.I. for Odds ratio	
			Lower bound	Upper bound
Dynamic range	0.024*	1.079	1.079	1.153

Table 2. Binominal logistic regression model for predicting likelihood of response based on pre dynamic range of hamstring muscles

Conclusion

Within this study R2-R1 of the MTS was a weak predictor of medium-term response to BoNT-A treatment for the hamstring muscles only. This was not the case for the other lower limb muscles injected including gastrocnemius muscle, where the predictive ability was limited and did not reach statistical significance.

We suggest that further research is required to evaluate the predictive ability of MTS to assist in the selection of patients for BoNT-A treatment. We would also recommend the inclusion of additional outcome measures to enhance the evaluation of the efficacy of BoNT-A treatment.



Use of the Quality Function Measure (QFM) to evaluate quality of movement in ambulant children with cerebral palsy following lower limb Botulinum Toxin A (BoNT-A) injections

Introduction

Quality of movement (QoM) is considered an essential component of effective gross motor skills in children with Cerebral Palsy (CP), influencing a child's level of activity and their participation opportunities. Interventions such as BoNT-A aim to optimize a child's functional skills and improve movement quality. However, there is little direct evidence to suggest that a reduction in dynamic spasticity following BoNT-A injections results in an improvement in movement quality. This prospective study evaluated the feasibility of introducing the QFM into an established clinical setting to assess short and medium-term changes in QoM in ambulatory children with CP following lower limb BoNT-A over a 12-month period



Figure 1: Examples of QFM items

Methods: 64 ambulant children with CP (34 female) requiring lower limb BoNT-A were recruited for the study. Gross Motor Function Classification System (GMFCS) levels of the children were: Level I = 22 Level II = 24 Level III = 18, mean age at injection was 7 years 5 months (SD 2y 8mo). The QFM was administered following a standardized protocol capturing performance in frontal and coronal planes. Children were encouraged to complete the test items according to individual ability. Videos of up to 3 trials of the GMFCS items in Dimensions D (13 items) and E (24 items) were taken at four specific time points pre, 6 weeks, 6 months and 12 months post BoNT-A treatment.

Results

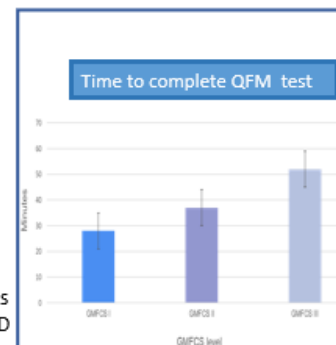
239 Video recordings were taken over a 12-month period, mean time to perform QFM test was 37 mins (range 25-60 mins) and differed between GMFCS levels; I=27.5 mins (SD 8.8 mins), II=35 mins (SD 6.1 mins), III= 48.8 mins (SD 7.4 mins).

Children in GMFCS level III completed fewer test items but took longer to complete the tests and exhibited increasing fatigue when asked to perform repeated trials.

Videos were subsequently scored for the 5 QFM attributes

- Alignment
- Co-ordination
- Dissociated movement
- Stability
- Weight shift.

Mean time to score each QFM was 46.78 mins (SD 11.43 mins) plus an additional 20 mins (SD 5mins) to input scores into system designed by QFM developers. Time for scoring was not significantly different between GMFCS Levels.



Time to score QFM videos	Whole Sample N=239	GMFCS Level I n=84	GMFCS Level II n=90	GMFCS Level III n=65
Mean minutes (SD)	46.78 (11.43)	45.56 (10.61)	46.89 (11.19)	48.13 (13.13)
Median minutes(IQR)	44.75 (38.94,54.38)	45.13 (38.75,53.63)	44.25 (38.94,51.00)	46.92 (38.38,46.92)
Min-max minutes	15- 90	25-90	24-75	15-79

Conclusion: The time taken to complete GMFM (37 mins) in the clinical setting and post clinic QFM analysis (47 mins) compares to other standardised tests such as the Assisting Hand Assessment which also require post clinic evaluation.

Introduction of QFM has proved acceptable in an established clinical setting as clinic times have been extended to accommodate this. However, it remains to be seen whether the amount of time for test administration and post clinic analysis and data inputting prohibits its use routinely in a clinical setting.

Katchburian, L.R.^{1,2,3}, Hodgson, X.¹, Crowe, B.¹, Oulton, K.³, Morris, C.⁴, Wray, J.³, Main, E.²Carr, L.J.¹

¹Neurosciences Unit, The Wolfson Neurodisability Movement Disorder Service, Great Ormond Street Hospital for Children, London, UK. ²Physiotherapy, University College London, Great Ormond Street Institute of Child Health, London, UK. ³ORCHID, Centre for Outcomes and Experience research in Children's Health Illness and Disability, Great Ormond Street Hospital for Children, London, UK. ⁴PenCRU Peninsula Childhood Disability Research Unit, University of Exeter Medical School, University of Exeter, UK.