The ASsessment and Physiotherapy managEment of Children with ataxia following surgical resection of posterior fossa Tumour (ASPECT Study)

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Abstract

Helen Hartley, Thesis submitted for PhD (FOHSC), ASPECT Study

Background

Up to 70% of children present with ataxia (balance and co-ordination problems) following surgical resection of a posterior fossa tumour (PFT). Physiotherapy is a conventional management approach, but few clinical research studies exist in this field to guide assessment and management.

Aims

1) Identify appropriate outcome measures to evaluate ataxia severity in children with PFT,
2) understand the current scope of physiotherapy practice and challenges to rehabilitation, and
3) determine the feasibility of conducting a randomised controlled trial (RCT) studying the effectiveness of virtual reality training (VRT) for balance in this population group.

Research Design

A mixed methods design consisting of four phases. Patient and Public Involvement was integral to all phases. Ethics approval was obtained.

Methods

Phase 1; Longitudinal observational cohort study examining the responsiveness of the Scale for the Assessment and Rating of Ataxia (SARA) and Brief Ataxia Rating Scale (BARS) and describing the natural history of ataxia in children with PFT.
Phase 2; Development and implementation of an e-survey to identify current international physiotherapy practice and challenges to rehabilitation.
Phase 3; Stakeholder workshops focused on the use of off-the-shelf VRT in children with PFT.
Phase 4; Mixed-methods (with embedded qualitative component) feasibility randomised controlled trial examining usual care versus VRT and usual care in children with PFT.

Results

Phase 1; Both the SARA and BARS appeared to reflect change in ataxia, with the SARA scale potentially more sensitive to subtle change. Children with medulloblastoma and midline tumours presented with more balance and coordination problems.
Phase 2; Ninety-six physiotherapists (12 countries) completed the e-survey. Treatment approaches varied but consensus relating to treatment intensity was identified. Challenges to rehabilitation included child and family factors, condition specific factors and service delivery factors.
Phase 3; Fifteen participants (children, their parents, innovators, physiotherapists) generated findings on engagement, practicality and utility of VRT for children with PFT and enabled game choice for Phase 4.
Phase 4; Ten children (aged 4-14 years), 1-3 years following surgery for PFT and nine parents participated. Recruitment was low (6%-40%, site dependent) but no issues with willingness for randomisation was identified. Assessment completion was high. Overall, the results suggest a future definitive trial may be feasible; however, adaptation to recruitment strategies are likely to be necessary.

Conclusion

Key findings include the responsiveness of the SARA, risk factors for severe ataxia and the identification of multifactorial challenges to rehabilitation. Initial information regarding the feasibility of conducting a formal randomised controlled trial examining VRT in children with PFT has been demonstrated, highlighting that further research is needed on trial protocol (including optimum timing and dosage of intervention) and core sets of outcome measures.

Original Contributions to Knowledge

The key original contributions to knowledge within this field are: (1) Identification of gaps in the evidence base; (2) advance knowledge of sensitivity of outcome measures; (3) mapping current physiotherapy practice; and (4) informing the design of future RCTs using VRT in children with PFT.

Key words: Paediatrics, Children, Rehabilitation, Neuro-oncology, Brain Tumour, Ataxia, Virtual Training, Outcome Measures, Feasibility, Balance

Declaration

I, Helen Hartley, confirm the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgments

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Contents

Glossary

Full Terminology	Acronym	Definition
Activities of daily living	ADL	Refers to functional tasks that are regularly carried out.
Barthel Index	Barthel	A 10-item outcome measure of activities of daily living for adults with rehabilitation needs e.g. stroke, inpatient and community rehabilitation.
Brief Ataxia Rating Scale	BARS	A 5-item scale which assesses severity of ataxia initially designed for use in the adult population.
Comparison of Ataxia Rating Scales Study	CARS	Study to examine the reliability and construct validity of the SARA and BARS subsequently amended to include longitudinal assessment at Alder Hey Children's Hospital led by H Hartley as Chief Investigator (CI).
Central Nervous System	CNS	Nervous tissue contained within the brain and spinal cord.
Cerebellar mutism syndrome	CMS	Characterised by delayed onset mutism/reduced speech and emotional lability after cerebellar or 4th ventricular surgery in children.
Clinical Doctoral Fellow	CDF	Individual research fellowship awarded by NIHR to clinicians who wish to obtain a PhD by research whilst developing their clinical skills.
Community Setting (or Local)	Community	Care delivered in a setting close to patients' home by a team based in that area (e.g. community base/education/home)
Ependymoma		Type of glioma tumour derived from ependymal cells. Can be slow or fast growing.
International Co-operative Rating Scale	ICARS	A 19-item scale (with four subscales; postural and gait, limb ataxia, dysarthria and oculomotor) to determine level of impairment due to ataxia in adults with cerebellar ataxia.
Low grade glioma	LGG	Slow growing tumour derived from glial cells.
Medulloblastoma		A fast growing (malignant/high grade) type of cancer that forms in the cerebellum. The most common high-grade tumour in childhood. They are a type of CNS Embryonal tumour (mass of rapidly dividing cells that begins in fetal tissue).

National Institute for Health and Clinical Excellence	NICE	National Institute with remit to provide guidance and advice to improve health and social care.
National Institute for Health Research	NIHR	National Institute with remit to fund health and care research involving patients and public in their work.
Pediatric Evaluation of Disability Index	PEDI	A three domain (mobility, self-care and social/communication) measure of functional ability for children aged 6 months to 7.5 years (Mobility domain includes 59 items).
Pediatric Quality of Life Measure	PedsQL	A quality of life measure for children/teenagers. The brain tumour module has 5/6 domains (age dependent, such as cognitive, pain, movement and balance, procedural anxiety, nausea and worry). It is adapted for age with parent report versions available from 2-18 and self-report from 5-18 years.
Posterior fossa tumour	PFT	Tumour in infratentorial region. This region is located below the tentorium. It contains the cerebellum and brain stem.
Public and Patient Involvement	PPI	Public and patient public involvement in research to ensure that research and outcomes are relevant to patients, carers and the public; research materials are easy to understand, and the research process is acceptable and sensitive to potential participants.
Scale for the Assessment and Rating of Ataxia	SARA	An eight-item scale which assesses severity of ataxia initially designed for use in the adult genetic ataxia population.
Tertiary Centre	Tertiary Centre	Highly Specialist Medical Care (including Principal Oncology Treatment Centre and Specialist Paediatric Neurosurgical Unit)
Work Package	WP	Work package refers to a sub project within the fellowship – considered as a ‘phase’ for the purpose of the thesis.

Chapter One - Introduction

Brain tumours are the most common group of solid tumours diagnosed in children, accounting for nearly a quarter of all childhood neoplasms worldwide, with approximately 500 new cases reported in children and adolescents in the UK per year (NHS Specialised Services 2010). Although prognosis has improved over the last 30 years, brain tumours remain the leading cause of tumour-associated death in children (Cancer Research UK Statistics 2018).

Surgical resection is a mainstay of management of children with brain tumours. For certain low-grade gliomas surgery e.g. cortical cerebral and cerebellar, surgery is often curative without the need for adjuvant therapy. For malignant tumours there is strong evidence that survival is influenced by the degree of resection (Jenkinson et al. 2018), and surgery is typically combined with further oncology treatment e.g. chemotherapy and radiotherapy as part of the child's management. However, surgery-related morbidity along with any subsequent oncological treatment should also be considered as having a potential impact on quality of survival. The NICE guidelines for improving outcomes in children and young people with cancer (NICE 2005, p68) identified that

> 'survivors of CNS malignancy are among the neediest of all cancer survivors, because of the effects of the tumour and multimodality therapy, all of which affect neurological, psychological, endocrine and academic function, and become more evident with increasing age'.

Despite this knowledge, the majority of the literature published previously has focused on survival (Albright et al. 1996, 2000, Bouffett et al. 2000, Birch et al. 2008), with event free and overall five-year survival figures commonly stated as key outcome indicators. However, in recognising the significance of treatment-associated morbidity, a second focus has evolved to report quality of life following survival (Di Rocco et al. 2010, Gerber et al. 2008, Bull et al. 2007). Although quality of survival is now recognised as important, there is still a

lack of understanding about physical and functional outcomes, and current research predominantly focuses on neuropsychological outcomes (Ris et al. 2013, Hanzlik et al. 2015, Camara-Costa et al. 2015).

Following surgical and medical management of their brain tumour, children are typically referred for rehabilitation including physiotherapy (NICE 2005), yet there is little evidence to guide physiotherapists on how best to assess and treat this population. In particular, children can present with mobility problems both as a result of the tumour and any surgical treatment (Di Rocco et al. 2010, Pruitt et al. 2011). The most frequent movement problem encountered by these children is ataxia which involves balance and co-ordination difficulties (Piscione et al. 2014, Hartley et al. 2018). Balance problems can be a significant challenge following initial treatment because of their impact on activities of daily life, return to school and participation with peers (Lannering et al. 1990, Piscione et al. 2014). It is therefore important to understand how physiotherapy can help in this area.

This study has been driven by uncertainties in clinical practice and inspired by children and their families. Working within this clinical area as a Specialist Paediatric Physiotherapist, I have become aware of the importance of rehabilitation in this patient group, and the challenges the children and their families face after their initial surgery, when the focus changes from survival to quality of survival. It can be difficult to answer the questions families ask regarding prognosis of return to function as this is an under-explored research area and limited evidence is available to guide physiotherapists. Equally, although therapeutic intervention is informed by clinical knowledge and applicable relevant research, the optimal type of physiotherapy intervention and delivery frequency is not clear, and these priorities are frequently raised by parents. A combination of these practice-related issues and the gaps in the literature led to my initial starting point for research in this area. To begin with I focused on assessment tools for this population group because accurate assessment using reliable outcome measures is the foundation for understanding the

effectiveness of interventions in research and practice. This original research was the CARS study, The Comparison of Ataxia Rating Scales in children with posterior fossa tumours. This then led to my interest in undertaking further research in this area, particularly considering the type and frequency of physiotherapy intervention, as my aim was to address concerns raised by families and also provide guidance for physiotherapists in an area where there is clinical uncertainty. This study combines clinical and family priorities in order to examine physiotherapy management of ataxia.

Each chapter of the thesis addresses a specific component of the work as can be seen in the following overview of the chapters.

In Chapter 1 I present the background and inspiration regarding the programme of work.

In Chapter 2 I discuss the current reporting of motor problems in children with brain tumours with a specific focus on children with PFT. The prevalence of ataxia in children with PFT is explored. I also highlight the need for accurate assessment of ataxia and critically review ataxia measurement scales. The lack of physiotherapy interventions for this patient group is also highlighted.

In Chapter 3 I present a literature review to map and critically evaluate the type, range and scope and scientific quality of physiotherapy interventions on impairment, function, participation and quality of life for children with ataxia.

In Chapter 4 I present the aims, objectives and design of each phase of the study and detail the involvement of families in the development of the research questions.

In Chapter 5 I present Phase 1 of the programme of work, examining the psychometric properties of the SARA and BARS scale in children with PFT. This phase was conducted with unpublished data from the CARS study (I conducted the CARS study prior to the PhD). The CARS study is introduced in this chapter.

In Chapter 6 I present the development and conduct of an e-survey of physiotherapists to determine current international practice regarding physiotherapy input for children with ataxia following surgical resection of a PFT.

In Chapter 7, using a narrative review, I discuss the evidence base and theoretical underpinnings regarding the use of virtual training in paediatric neuro rehabilitation. In the second part of the chapter I then present the development and conduct of two workshops involving children, their parents, physiotherapists and gaming innovators to identify games that could be used in the feasibility randomised controlled trial.

In Chapter 8 I present the planning and implementation of a mixed methods feasibility RCT, to determine the feasibility of conducting a fully scaled RCT examining the effectiveness of virtual reality training in children with ataxia following surgical resection of a PFT.

In Chapter 9 I present and evaluate the original contribution to knowledge I have made based on my programme of work. Also, I present a synthesis and critical discussion of the results in relation to the overarching research question. I explore the strengths and limitations of the study and present my recommendations for future research and practice.

The programme of work is complex, and Figure 1.1 has been developed to illustrate the components of the thesis and demonstrate the crucial involvement of supporting partners such as the Steering Group and Patient and Public Involvement (PPI) groups.

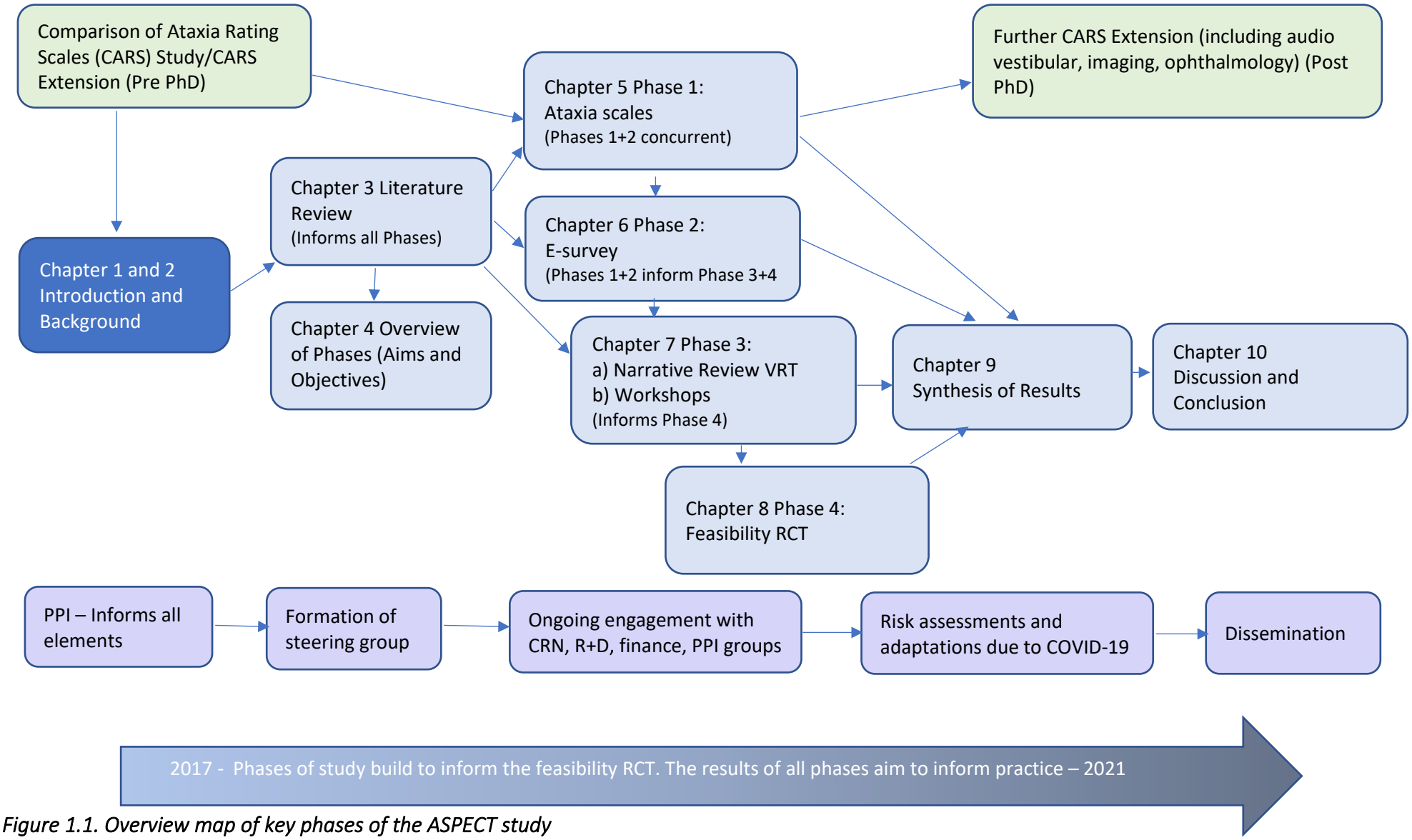

Figure 1.1. Overview map of key phases of the ASPECT study

Chapter Two - Motor impairment in children with posterior fossa tumours

2.1 Introduction

This chapter presents a narrative review discussing the current reporting of motor problems in children with brain tumours and then focuses on children with posterior fossa tumours. The prevalence of ataxia in children with this tumour type will be explored highlighting the significance of this problem. The need for accurate assessment of ataxia will also be discussed and ataxia measurement scales will be critically reviewed.

The chapter then moves on to highlight the lack of evidence for physiotherapy interventions for this patient group.

2.2 Prevalence of motor impairment in children with brain tumours

Motor deficits are common in children with brain tumours (Pruitt et al. 2011). Sonderkaer et al. (2003) reported that nearly 70% (n=45) of 65 children had long term neurological deficits following treatment of a brain tumour, with 35% (n=23) of children having severe problems such as ataxia, weakness or alteration in muscle tone. Gerber et al. (2008) in a smaller study of 11 children diagnosed under the age of one year, noted that 82% (n=9) of children presented with motor problems, although the measurement process and definition of motor deficits were not clearly described. Impaired balance and coordination, hemiplegia, and cranial nerve palsies can have a significant impact on functional independence, participation in recreational activities and reintegration into education (Pruitt et al. 2011, Fountain & Burke 2017). However, the few studies that have focused on motor outcomes for children with brain tumours have typically presented the incidence of motor deficits (often without

the use of standardised measures) and little is known about how motor impairments change over time and how these changes might impact on functional recovery.

Lack of standardised assessment and reporting of motor deficits in this population is a significant issue not only in clinical practice but also for clinical trials that aim to reduce the impact of motor impairment in children's lives. These limitations reduce confidence in the accuracy of the assessment and the prevalence of motor impairment reported. Children with brain tumours can present with problems both as a result of the tumour itself or subsequent to surgery or other oncology treatments, therefore standardized assessment tools and the identification of motor problems are vital in this population to determine which element(s) may have influenced the child's presentation. Standardised assessments can also be used to track changes following interventions to demonstrate improvement or deterioration of skills over time which has not previously been reported.

In the next section I will focus on literature that has considered children with posterior fossa tumours as a distinct group and the movement problems that can be seen in this population group.

2.3 Posterior fossa tumours and prevalence of ataxia

Childhood brain tumours are described according to their anatomical location, tumour histology and molecular subtype. Posterior fossa tumours (PFT) describe those originating in the posterior fossa region. They may have different histologies e.g. low-grade gliomas (slow growing tumour) and medulloblastomas (a fast-growing tumour), named according to the cells they derive from. PFT account for approximately 50% of all childhood brain tumours (Ostrom et al. 2014).

Management of PFT typically involves surgical resection, solely or in combination with adjuvant oncology treatment such as radiotherapy (use of ionising radiation to damage cancer cells) or chemotherapy (use of cyototoxic agents to damage or prevent cancer cells

from dividing). Children with PFT have a distinctive set of issues including rapid onset of ataxia, hydrocephalus, increased intra-cranial pressure and potential for deterioration in the immediate post-operative period, in addition to potential problems from any subsequent oncological management such as radiotherapy. These specific problems are related to the location of the tumour and influence on adjacent structures. Children with PFT may also demonstrate a surgical complication known as cerebellar mutism syndrome (CMS), which affects speech and emotional lability in the post-operative period (Gundrunardottir et al. 2016). Figure 2.1 illustrates exemplar pre- and post-operative images of a posterior fossa tumour.

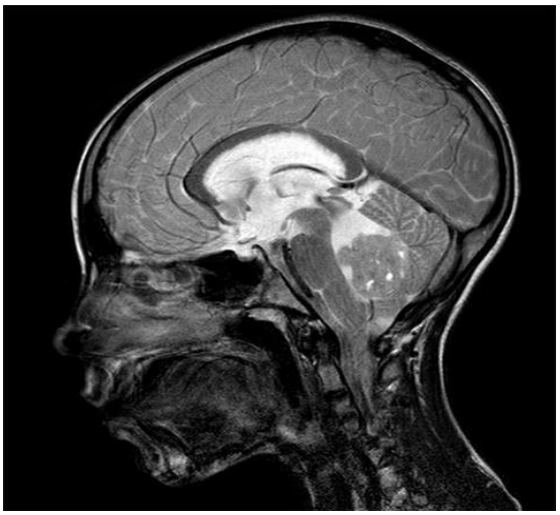

Image a; Pre-operative PFT (medulloblastoma)

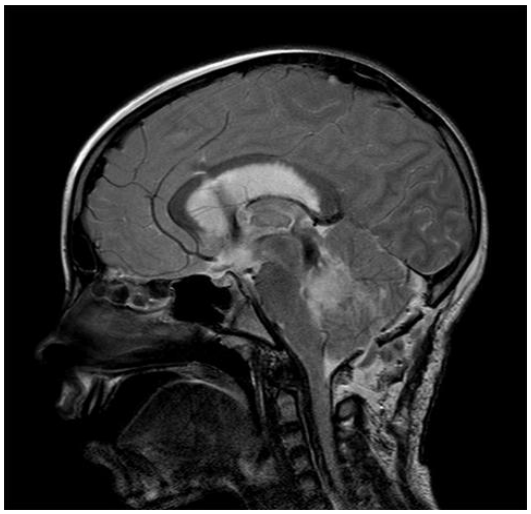

Image b; Post-operative scan

Figure 2.1. Example MRI images of a posterior fossa tumour in childhood (pre and post-operatively, image used with permission)

The posterior fossa region describes a complex anatomical area below the tentorium which includes the cerebellum, brainstem and cranial nerves (Isik & Ozek 2015). It extends from the tentorium (through which it communicates with the supratentorial space) to the foramen magnum (through which it communicates with the spinal canal) and is situated at the outlet of the cerebrospinal fluid flow from the ventricular system (Seker & Rhoton 2015). The anatomy of the cerebellum in relation to the cerebral hemispheres is illustrated in Figure 2.2.

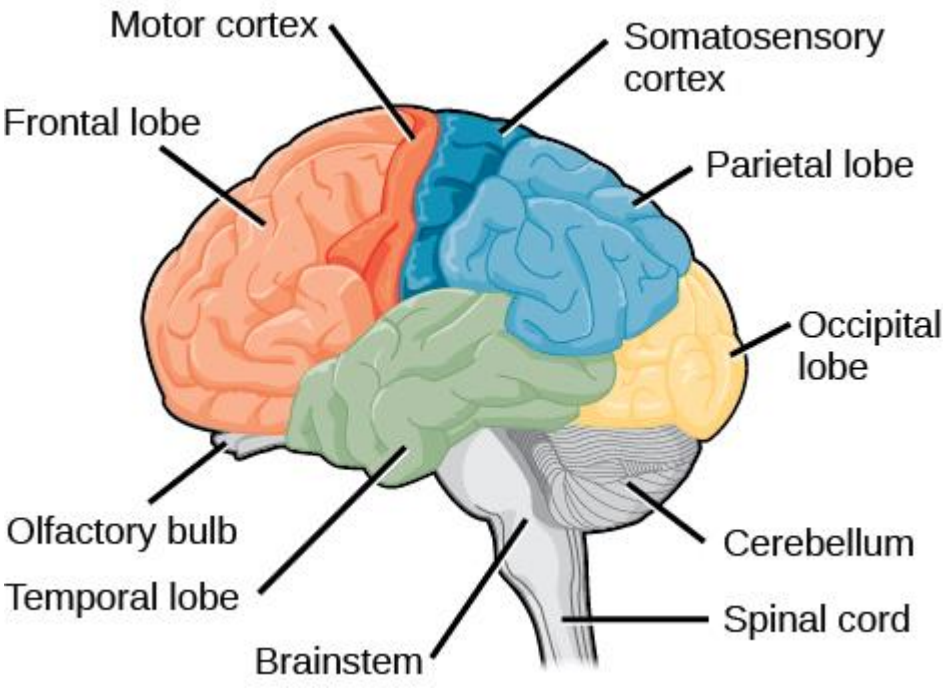

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Figure 2.2 Anatomy of the brain (sagittal view)

Ataxia is the predominant motor problem in children with posterior fossa tumours (Cochrane et al. 1994, Di Rocco et al. 2010). Ataxia can describe a related number of impairments including reduced limb coordination, balance, gait difficulties, eye movement issues and speech problems (Fonteyn et al. 2014). Ataxia is reported as a presenting sign in 58% (n=23) of 41 children (Di Rocco et al. 2010) to 80% (n=52) of 65 children (Sonderkaer et al. 2003) with PFT. This variation in incidence of ataxia pre-operatively may be due to differing assessment procedures or the impact of tumour location in the specific study populations. Di Rocco et al. (2010) used a non-validated assessment of cerebellar signs alongside the Movement ABC outcome measure. Sonderkaer et al. (2003) did not specify the method in use and a variety of approaches could have introduced error. Wilne et al. (2007) presented a systematic review and meta-analysis with pooled data from five studies with children with PFT (n=476) reporting that 60% (n=285) of 476 children demonstrated ataxia pre-operatively, although there was no standardisation across the studies.

The presence of pre-operative ataxia is related to the location of the tumour in the cerebellar region with damage to the deep cerebellar nuclei particularly thought to influence ataxia (Konczak et al. 2005, Konczak & Timman 2007). Figure 2.3 illustrates the central vermis of the cerebellum and the two lateral hemispheres.

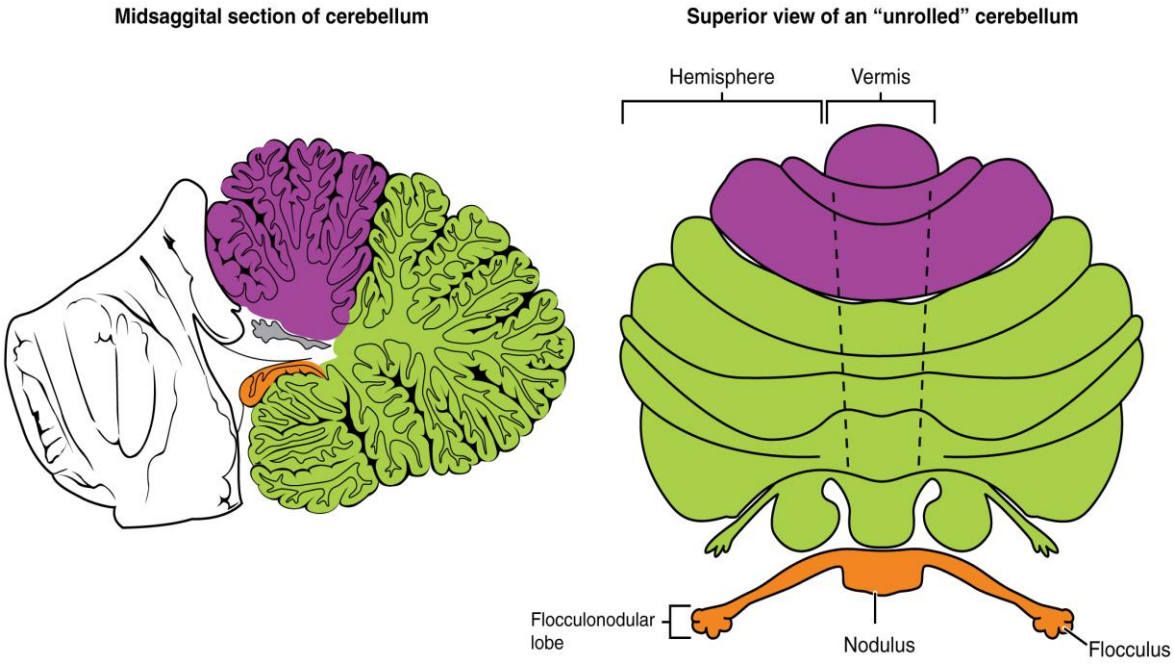

Image freely available from https://opentextbc.ca/anatomyandphysiology/wp-content/uploads/sites/142/2016/03/1613_Major_Regions_of_the_Cerebellum-02.jpg

Figure 2.3 – Anatomy of the cerebellum (superior view of an 'unrolled' cerebellum)

Figure 2.4 demonstrates further detail indicating the location of the deep cerebellar nuclei: the fastigial, interpositus (comprises globose and emboliform) and dentate nuclei, and the lobes of the cerebellum.

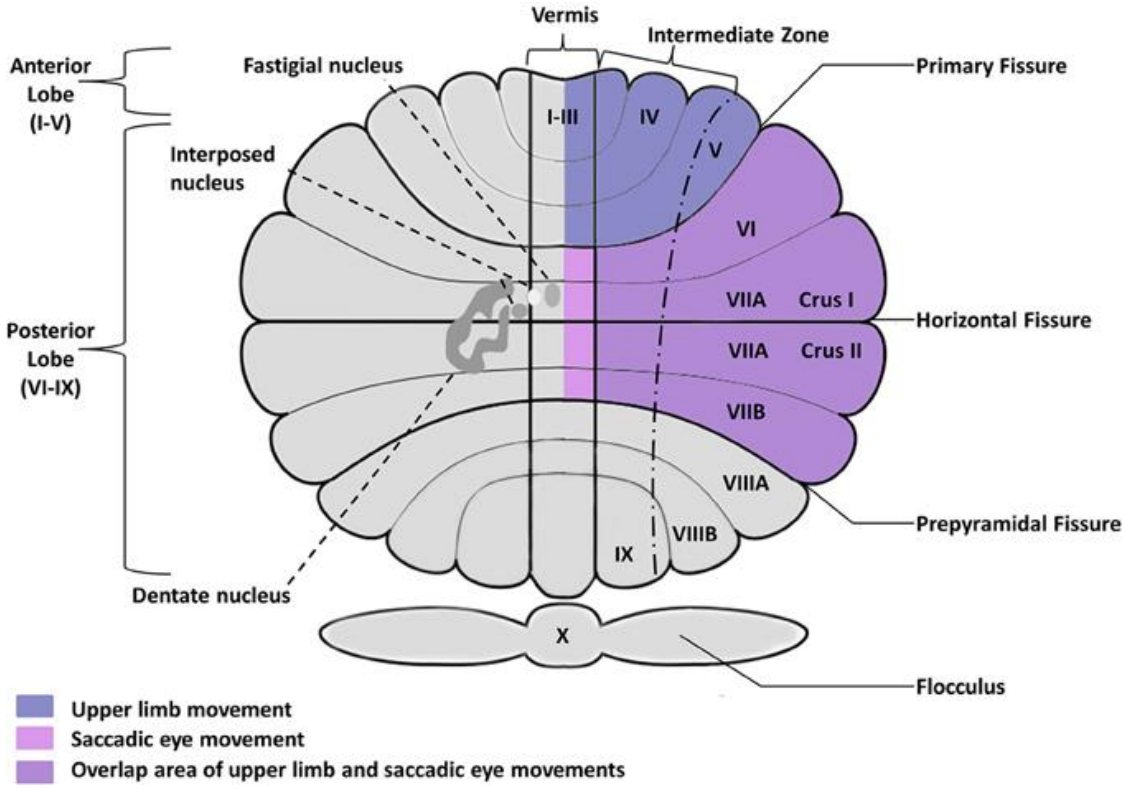

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Figure 2.4 Illustration of the anatomical lobes of the cerebellum

Although commonly reported, it is difficult to determine the severity of ataxia and any change following surgery or intervention, due to a lack of consistent assessment and documentation. Cochrane et al.'s (1994) retrospective review described an increase in deficit (typically ataxia) in 40 (38%) out of 105 patients (aged 1-16 years) following surgery for posterior fossa tumour resection. However, it is not clear how the deterioration was measured as no details were provided about how a neurological deficit was defined or how the assessment took place. Bull et al. (2014) noted similar incidences of truncal ataxia (affecting the ability to maintain normal posture of the trunk) both pre- and post-operatively in low (20% (n=7 of 35 children) pre and 23% (n=8 of 35 children) post-operatively), and high-grade tumours (62% pre (n=23 of 37 children) and 65% (n=24 of 37 children) post-operatively respectively). However, as the extent of ataxia was not reported, it is unclear if there was any change in severity pre to post-operatively.

More recently, studies have begun to use standardized outcome measures to assess ataxia, balance and co-ordination problems. Piscione et al. (2014) found 70% (n=21) of 30 children with PFT had long term balance problems post operatively and used standardized balance scales (BOT-2) to determine their assessment findings. This is in keeping with recently published data from the Comparison of Ataxia Rating Scales Study (CARS study) (Hartley et al. 2018). This study initially assessed the reliability of ataxia rating scales and was subsequently extended to include longitudinal assessments led by myself as Chief Investigator (pre-doctoral) as detailed further in Phase 1. We found that 71% (n=30) of 42 children with a posterior fossa tumour (aged 5-18) presented with ataxia over 12 months following surgical resection (Hartley et al. 2018). Although there is only a small body of literature in this area, there is agreement about the high incidence of ataxia in children with PFT.

2.4 Risk factors for long term/increased severity of ataxia

There is evolving evidence regarding the long-term nature of ataxia in children with PFT. Sonderkaer et al. (2003) identified that 55% (n=36) of 65 children who had ataxia at presentation continued to have ataxia at the point of long term follow up (up to 10 years post diagnosis), although there were no standardized outcome measures used in the assessment. Robertson et al. (2006) completed a prospective study (which has the advantage of ensuring consistent documentation) of post-operative problems in 450 children (median age 6 years, range not reported) with medulloblastoma. The authors observed that 92% (n=414) of 450 patients who were classified as having severe ataxia (defined as persisting over four weeks), continued to have ataxia at a one-year follow-up assessment. Although Robertson et al. (2006) did not clearly describe the measurement of ataxia, their study provides preliminary information about the potential long-term nature of ataxia following resection of medulloblastoma. Ataxia can also be an issue in children with low grade gliomas (LGG) with Aarsen et al. (2006) noting that 53% (n=20) of 38 participants

with cerebellar LGG presented with ataxia at follow up assessment although again the assessment process was not clearly documented. This evidence of long-term ataxia is supported by the recent studies as noted above (in section 2.3) by Piscione et al. (2014) and Hartley et al. (2018) which used standardised outcome measures to demonstrate the potential for long term ataxia. Indeed, Hartley et al. (2018) in the CARS study also demonstrated that 57% (n=24) of 42 participants continued to undergo physiotherapy for two years or more post-surgery, highlighting the ongoing impact of balance and co-ordination problems.

Although not examined in as much depth as neuropsychological outcomes, there is some emerging evidence regarding potential risk factors for increased severity and long-term ataxia. The CARS study (Hartley et al. 2018) noted that children with medulloblastoma, those with midline tumour location, those diagnosed with CMS, and those who underwent adjuvant radiotherapy and chemotherapy demonstrated higher ataxia scores (assessed using ataxia rating scales). There was no effect of age at diagnosis on ataxia scores. Piscione et al. (2014) and Rueckriegel et al. (2009) concurred that children with malignant tumours and those with tumours infiltrating the vermis demonstrated poorer balance outcomes measured by different ataxia/physical function assessment tools.

Tumour location appears to be a significant factor in the presence of long-term ataxia. Kuper et al. (2013) and Konczak et al. (2005) both suggested that damage to the deep cerebellar nuclei is implicated in persistent impairment. These studies mapped ataxia assessment (using the International Co-operative Ataxia Rating Scale (ICARS)) with imaging findings. The results provided further evidence that involvement of the different cerebellar nuclei can result in specific types of impairment, e.g., the nuclei fastigial (NF) may be particularly involved with postural control resulting in balance disorders, whilst the nuclei interpositus may be responsible for upper limb ataxia. Puget et al. (2009) agreed that damage to the dentate nuclei and the inferior vermis in children with PFT are predictors of neurological

deficit, in particular fine motor skills. This links with other work which has mapped the function of the cerebellum into regional areas (Manto & Marien 2015, Guell & Schmahmann 2020). This recent work on the function (physiological divisions) of the cerebellum, aims to understand the connections with the cerebellar cortex and the supratentorial region whilst detailing potential functions of specific areas of the cerebellum. An illustration of mapping of cerebro-cerebellar circuits is illustrated in Figure 2.5.

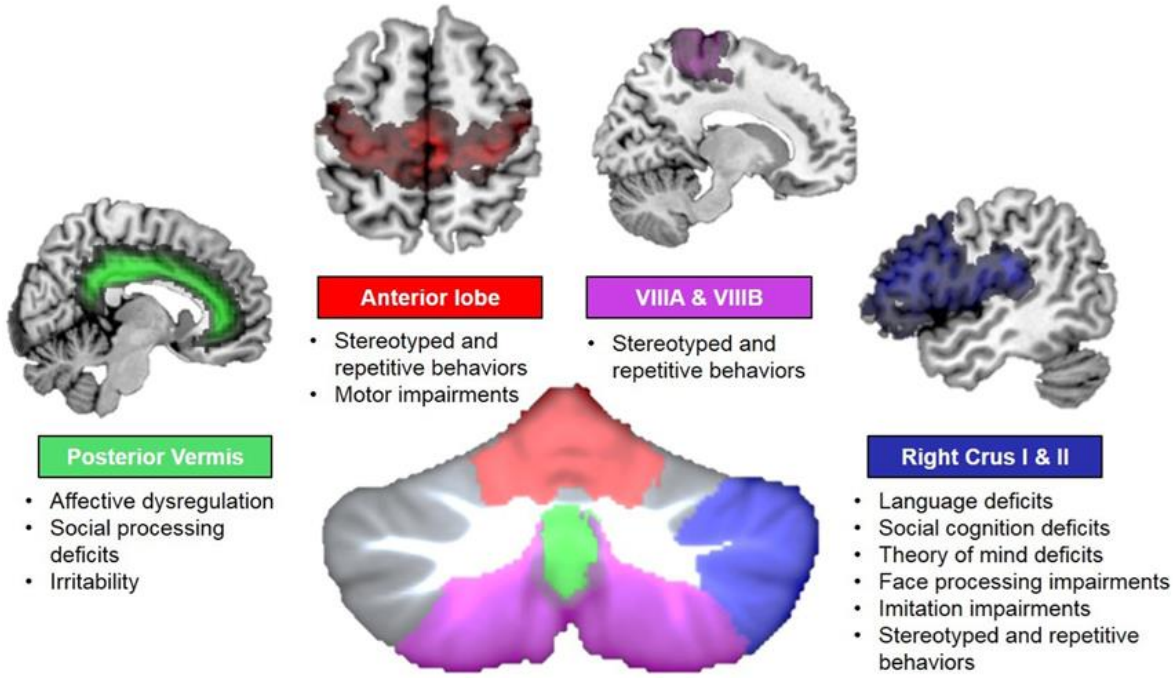

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Figure 2.5 Cerebro-cerebellar circuits

In summary, the literature suggests that ataxia commonly occurs as a presenting sign and may increase in severity post-surgical resection of PFT. Preliminary risk factors associated with ataxia severity have been identified, however, there is a lack of detail regarding how ataxia is assessed along with limited use of standardized outcome measures making it difficult to compare studies and to draw definitive conclusions. The long-term impact of ataxia on children and their families is becoming increasingly recognized by clinicians and physiotherapists, and the subsequent effect on functional ability and participation is also

more widely reported in the literature (Wilson et al. 2015). Therefore, it is important to consider how best to accurately assess children presenting with ataxia and then provide them with the optimal physiotherapy input to help maximize their rehabilitation potential.

The use of outcome measures in children with PFT will now be discussed including the challenges to their use in practice.

2.5 Challenges in measuring outcome in children with posterior fossa tumours

Outcome measures are used by physiotherapists to identify progress and to provide evidence of the effectiveness of rehabilitation (Marciniak et al. 2001). They can also provide a pre-operative baseline to provide information regarding the impact of surgery and any subsequent medical interventions. As highlighted in the previous section, one of the particular difficulties with assessing motor outcomes in children with posterior fossa tumours is distinguishing between the damage caused by the tumour, the secondary effects of increased intracranial pressure, and the consequences of interventions such as surgery or adjuvant oncology treatment (Piscione et al. 2014). Additionally, with this patient group, clinicians are challenged with planning oncology treatment protocols informed by previous research studies e.g. balancing whether complete resection should be aimed for whilst considering the impact of surgery on quality of outcome. Therefore, for planning purposes an accurate measure of morbidity that includes motor outcomes is also crucial. However, the characteristics of this population group mean that developing and/or selecting an outcome measure is challenging. In order to measure change along the child's journey from pre-operative presentation to completion of treatment, the use of the same outcome measure would mean it would require the ability to be completed quickly in an acute environment when the child might be medically unstable, whilst also reflecting change later in their rehabilitation. Also, it is essential that outcome measures not only provide clinicians with accurate information regarding improvement and/or deterioration but that they can reflect change that is meaningful to the child and their family. These challenges mean that

there is no specific validated measure that has been shown to be suitable across the timeline and which meets all the requirements, and this has resulted in researchers selecting a range of non-specific outcome measures, based on their preference. Presently there is a lack of outcome measures specifically designed to be used for children with brain tumours with ataxia.

The only currently standardised specific outcome measure for children with brain tumours is a recently adapted version of the PedsQL; the Paediatric Quality of Life Inventory, PedsQL™ Brain Tumor Module (Varni et al. 1998, Palmer et al. 2007). The PedsQL™ Brain Tumor Module is a modular self (or parent) reporting tool looking at health related quality of life that has one section that considers 'movement and balance'. However, the movement section only contains three questions which, although possibly useful as part of the overall tool to measure quality of life later post diagnosis, would not be detailed enough to determine change in the acute stages where children may be severely affected.

Outcome measures are used in practice to assess function in children within the wider context of acquired brain injury (ABI), which would include children with neurological issues following diagnosis of a brain tumour. However, to date, the only tool that is specifically validated in children with ABI is the PEDI (Pediatric Evaluation of Disability Index) developed by Haley et al. (1992) which has mobility, self-care and social interaction domains. Although not specific to ataxia it can be used across the rehabilitation team to assess functional change.

The Bruininks-Oserestsky Test of Motor Performance (BOT-2) (Deitz et al. 2007) has also been used to describe physical function in children with acquired neurological problems. It was initially designed and evaluated in children with developmental coordination disorder (Bruininks and Bruniniks 2005) and has the advantage of being normative referenced. It includes fine motor, manual coordination, body coordination and speed, strength and agility sections which would be of interest in this population group. However, this outcome

measure may not be appropriate for use in the immediate pre and post-operative stage as it takes approximately 20 minutes to complete and includes items such as running and strength tests which would potentially be very difficult and/or unachievable in children with significant difficulties in the acute stage of their presentation. Therefore, exploration of this outcome measure is outside the scope of this study, as identification of an outcome measure that could be completed quickly at all stages of a child's presentation was the initial priority.

Overall, it is difficult to select tools that focus on the particular challenges for children with posterior fossa tumours who primarily present with ataxia as their motor deficit. The next section of the chapter focuses on available ataxia rating scales that could be used as outcome measures as a quick assessment that can be completed throughout the child's journey perhaps in combination with additional participation-based measures when indicated. In the following section the outcome measures specifically designed to assess ataxia will be critically evaluated.

2.6 Ataxia measures

Measurement scales have been developed to longitudinally measure ataxia and evaluate interventions for adult populations and individuals with genetically diagnosed cerebellar disease. These are used by clinicians as an outcome measure based at the impairment level that is, measures with a focus on a body function problem according to the International Classification of Functioning, Disability and Health (ICF) (WHO 2001).

The International Co-operative Ataxia Rating Scale (ICARS) (Trouillas et al. 1997) is one of the most well-known ataxia scales. It is a 100-point scale with a higher score representing greater impairment. It was initially developed for the purpose of planning and developing clinical trials in hereditary ataxias in adults. It is reported to have excellent inter-observer reliability (Herndon 2006), and more recently it has been shown to be sensitive to change

in non-degenerative conditions (e.g. surgical and ischaemic lesions), however, its ability to detect a change in chronic conditions is less well supported (Schoch et al. 2007, Morton et al. 2010). It is still only predominantly used in the adult genetic ataxia population although a small study by Sival and Brunt (2009) looked at normative data in children, carrying out the assessment in healthy children (4-14 years). They found that ICARS scores improved with age from a score of 13 at four years of age, to the adult optimum of 0 at thirteen years, although specific details regarding testing conditions were not clearly reported. The findings of this study highlight the importance of applying age specific paediatric reference values alongside carefully designed control studies if longitudinal interpretation of the ICARS is required. No further literature evaluating the use of the ICARS in children in terms of examining psychometric properties has been identified.

In clinical practice, the ICARS is not widely used in paediatrics, possibly as it is a lengthy tool (19 items), which could be particularly difficult where engagement and compliance with assessment procedures can sometimes be a challenge for younger children. This is particularly relevant in the PFT population where initial assessment may occur 24-48 hours post-surgery when assessment needs to be quick in view of potential issues such as medical stability, pain, irritability and alertness which can affect the child's tolerance to assessment. There is often only a short window for physiotherapists to access the child pre-operatively, again necessitating a timely assessment as surgical resection is often an emergency procedure. In this limited pre-operative timeframe there is also the requirement for assessment by other professionals, e.g. ophthalmology and neuropsychology, alongside time needed for extensive imaging to assist with surgical planning.

The two scales that are most commonly described and used both clinically and within research (predominantly in the adult field, to date) are: the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hubsch et al. 2006) and the Brief Ataxia Rating Scale

(BARS) (Schmahmann et al. 2009). These scales will be discussed individually in the next sections of this chapter.

2.6.1 Scale for the Assessment and Rating of Ataxia

The Scale for the Assessment and Rating of Ataxia (SARA) (Appendix 1) was developed by a group of European neurologists from a semi-quantitative assessment of cerebellar ataxia in adults with a form of genetic ataxia known as spinocerebellar ataxia (SCA) (Schmitz-Hubsch et al. 2006). The scale is based on the normal standard neurological examination for co-ordination and requires no equipment. It has eight items to score (total cumulative score 40) with a higher score reflecting more severe ataxia. Schmitz-Hubsch et al. (2006) presented the initial development of the tool with a series of stages reported. Initially they compared SARA scores with ataxia disease stage (indicating ataxia disease stage in relation to progression of genetic ataxia), the ICARS and the Barthel Index (an adult measure of function/activities of daily living (ADL)) to examine validity of the tool. The initial version of the SARA included an item scoring oculomotor symptoms. However, internal consistency was higher when this item was omitted therefore, the oculomotor item was removed from the scale.

The modified version was subsequently compared with ataxia disease stage, the Barthel Index and the Unified Huntington's Disease Rating (UHDRS-IV) (Seisling et al. 1998). A correlation was shown with all these elements demonstrating construct validity using a number of variables. Schmitz-Hubsch et al.'s (2006) study included a similar number of control participants without a diagnosis of spinocerebellar ataxia which provided some normative data. Only 79% of the controls scored 0 on the scale with a range of 0-7.5; however, the mean and standard deviation is presented as 0.4±1.1. Inter-rater reliability was also examined in a small subset of participants though it was reported to be very high (ICC 0.98).

This scale has been translated into other languages including Brazilian Portuguese (Braga-Neto et al. 2010) and Japanese (Sato et al. 2009) and is also now being used in other ataxic syndromes such as Friedreich Ataxia (Burk et al. 2009) and with people with ataxia following stroke (Kim et al. 2011). Burk et al. (2009) demonstrated high construct validity of SARA items when correlated with the ICARS in patients with Friederichs's ataxia (a genetic condition); this study included a younger population, with some children in the sample, though the number is unspecified. Weyer et al. (2007) studied a population with various ataxia disorders where 64 adult patients were all rated independently by two investigators and again inter-rater reliability was very high (ICC 0.98) and the scale also correlated with the Barthel Index in this population. Weyer et al. (2007) also looked at the inter-rater reliability of each item, and this was again high (all ICC >0.79). Yabe et al. (2008) also demonstrated that the SARA only took a third of the time that the ICARS assessment took to carry out although their study did not detail the level of experience of the clinicians carrying out the assessments.

Overall, all the studies focusing on the psychometric properties of the SARA in the adult population agree that it demonstrates high inter-rater (and intra-rater) reliability in the populations tested, with correlation with activities of daily life scales. Correlation has also been demonstrated with disease stage although sensitivity to change was not initially explored when the scale was originally developed (Schmitz Hubsch et al. 2006). However, Schmitz-Hubsch et al. (2010) subsequently looked at the longitudinal properties of the scale indicating that the tool is responsive to change, also reporting a minimally clinically important difference of 1.1 providing further evidence for the usefulness of this tool. Lee et al. (2011) also examined SARA scores longitudinally and observed a correlation with disease duration (genetic adult ataxia) suggesting that the SARA score could be used to measure disease progression and thus is of value in longitudinal research.

The COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) tool (Mokkink et al. 2010a) provides a checklist for determining the quality of studies/literature on the measurement properties of health measurement instruments. In combination, the collection of studies carried out on the SARA fulfil most of the COSMIN tool's requirements in terms of internal consistency, reliability and responsiveness. However, some elements on the checklist, such as missing data, are not mentioned in the articles and the absence of reporting these elements reduce confidence in the quality of the study results. In comparison to the number of validation articles on the BARS, the SARA has more evidence for its use in the clinical setting. It is noted both scales were developed by clinicians and there is no mention regarding any participant/patient feedback with respect to the administration of the tool e.g. choice of wording for instructions for participants. A comparison of the SARA and BARS is presented in Table 2.1. Further analysis of the SARA and BARS scales will be presented in Chapter 5 (Phase 1 of this programme of work) and reference will be made to the COSMIN checklist. Overall, the SARA appears to have some qualities that would make it useful in acute paediatrics, e.g., its ease of use with a short assessment based on the normal clinical examination of coordination along with the demonstrated qualities of reliability, validity and sensitivity to change.

2.6.2 Brief Ataxia Rating Scale

The BARS (Appendix 2) was based on a modified version of the ICARS and has five items. Scores are added to give a total out of 30. The five items are again based on elements typically used to assess coordination in clinical practice. Schmahmann et al. (2009), in the primary published paper on this tool, argue that the BARS is of equal value to the SARA in its correlation with ICARS and is quicker to carry out. Schmahmann et al. (2009) developed the BARS initially using healthy controls to gain information on normative data. They chose to retain an oculomotor item in the scale despite reporting a lower internal consistency when this item is included, stating that identification of eye movement difficulties is an important part of the clinical picture. The authors argued that this actually indicates that the scores of

limb co-ordination, gait and articulation cannot accurately predict the oculomotor score, and therefore, alongside being clinically important, it is of value to have an oculomotor item within the scale. The other items of the BARS are similar to those of the SARA and include assessment of gait, upper limb co-ordination (finger to nose test), lower limb co-ordination (heel-shin test) and a speech item. It is noted that for this scale the left and right limb scores are considered separately and contribute to the total score, whereas with the SARA the left and right limb scores are averaged. Schmahmann et al. (2009) also reported high inter-rater reliability (ICC 0.91), although the responsiveness of the BARS has not yet been demonstrated. As the responsiveness of this scale has not been determined, the study by Schmahmann et al. (2009) which presents the BARS does not fulfil as many COSMIN tool criteria as the studies on the SARA. The BARS has now also been translated into Brazilian Portuguese (Camargos et al. 2016) and Turkish (Arslan et al. 2019).

The consistent use of validated outcome measures, such as these scales, should help facilitate comparison across intervention studies in addition to providing an accurate baseline measure and a record of change. Despite the development of validated outcome measures for adults with a genetic ataxia, there have been no equivalent scales specifically designed for children. However, there has been recent work to evaluate the use of the SARA and BARS in paediatrics which will be discussed in the following section. Elements of this research have been carried out at as part of the CARS study (as highlighted in section 2.2), and further evaluation of the potential validation and use of these scales in children and young people with posterior fossa tumours was the aim of Phase 1 of this programme of work.

Table 2.1 Presentation of the SARA and BARS ataxia rating scales

Outcome Measure/ Author, year, Aim	**Measured Attributes**	**Population**	**Comments**	**Evidence**			
				Reliability	**Validity**	**Internal consistency**	**Responsiveness**
SARA (Schmitz-Hubsch et al. 2006) To assess the severity of ataxia.	8 items. Gait (0-8 points), Stance (0-6 points), Sitting (0-4 points), Speech (0-6 points), Finger chase (0-4 points), Nose-finger test (0-4 points), Rapid alternating hand movements (0-4 points), Heel-shin slide (0-4 points). Score added up out of 40. Left and right limb scores averaged.	Spinocerebellar ataxia.[1, 2] Ataxic Stroke.[3] Friederichs Ataxia.[4] Children with posterior fossa tumours.[5] Early onset ataxia (EOA).[6]	Based on normal exam of co-ordination. Quick to carry out.[7] No eye item included. Translated into Brazilian Portuguese[8] and Japanese.[9] Age dependency reported in children.[10] Normative data available in children.[11]	Reliability demonstrated in: Adults with SCA;[1, 2] Healthy children; [10,11] Children with PFT; [5] Children with EOA. [6]	Validity (construct) demonstrated in: Adults with SCA (against ICARS and Barthel);[1] Adults with FA (against ICARS and FARS);[12] Children with PFT (against the PEDI);[5] Adults with ataxic stroke (against BBS);[3] Children with early onset ataxia.[6]	Reported in original study[1] and in healthy children population.[11]	Reported in adults with SCA.[1] MCID reported as 1.1.
BARS (Schmahmann et al. 2009)[13]	5 items. Gait (0-8 points),	Mixed cerebellar disorders including	Based on normal exam	Reliability demonstrated in:	Validity (construct) demonstrated in:	Reported in original study[13] and in	Not reported

To assess the severity of ataxia.	Heel shin (0-4 points), Nose-finger test (0-4 points), Speech (0-4 points), Oculomotor (0-2). Score added up out of 30 Left and right limb scores combined.	hereditary e.g. SCA and FA and acquired disorders e.g. stroke/ cerebellitis.[13,14] Children with posterior fossa tumours.[5]	of co-ordination. Quick to carry out.[5] Translated into Brazilian Portuguese[14] and Turkish.[15] Age dependency reported in children.[10]	Adults with mixed cerebellar disorders;[13,14] Healthy children;[10] Children with PFT.[5]	Adults with mixed cerebellar disorders (against MICARS and SARA);[13,14] Children with PFT (against the PEDI).[5]	healthy children population.[10]	

References: [1] Schmitz-Hubsch et al. 2006, [2] Weyer et al. 2007, [3] Kim et al. 2011, [4] Burk et al. 2009, [5] Hartley et al. 2015, [6] Brandsma et al. 2017, [7] Yabe et al. 2008, [8] Brago-Nero et al. 2010, [9] Sato et al. 2009, [10] Brandsma et al. 2014, [11] Lawerman et al. 2017a, [12] Saute et al. 2012, [13] Schamahmann et al. 2009, [14] Camargos et al. 2016, [15] Arslan et al. 2019 (References numbered for purpose of table, for full references please see Reference list).

2.6.3 SARA and BARS in paediatrics

Research, led by the European Ataxia Group, has assessed the validity and reliability of the SARA and BARS in the paediatric population. A pilot study in healthy children (n=52) by Brandsma et al. (2014) reported high reliability for the SARA and BARS (ICC 0.81, ICC 0.70 respectively). The effect of age on the outcome measures was also explored with an adult optimum score reached by the age of 10 for the SARA scale and 11 years for the BARS, indicating the effect of age on assessment of coordination. This was subsequently followed by a large multicentre European study in association with the European Ataxia Group (n=156, with raters from 13 European countries) examining the reliability of the SARA and presenting normative values (Lawerman et al. 2017a). This larger study confirmed that the SARA score is age dependent in healthy children and reported a slightly lower inter-rater reliability than the pilot study (ICC 0.63) (Lawerman et al. 2017a). The most significant variance was demonstrated in children between the age of four and seven. The CARS study demonstrated excellent inter-rater reliability of both the SARA and BARS in children with posterior fossa tumours (Correlation coefficient 0.94 and 0.91 respectively) and a good correlation between the scales and the mobility domain of the Paediatric Evaluation of Disability Index (PEDI) (r=0.77 and r=0.76 respectively), illustrating one aspect of construct validity (Hartley et al. 2015). It is noted that this was a single site study with three raters who had undergone joint training, potentially leading to lower variability in scoring. All the children were aged nine years or over which is likely a significant factor in the higher reported reliability which is similar to that reported in the adult papers. The responsiveness of these scales in this population group is yet to be demonstrated and was considered in Phase 1 of this programme of work. There has also been recent evaluations of the use of the SARA in early onset ataxia (40 participants, age range 5 to 34 years) with high inter and intra-rater reliability and construct validity reported (Brandsma et al. 2017, Lawerman et al. 2017b), although discriminant validity in terms of identifying ataxia in younger children was low.

Identifying a reliable, valid and sensitive tool in this population group will enable these outcome measures to be readily integrated into practice, as it is recognized that psychometric properties including validity, sensitivity, reliability and feasibility should be assessed in the specific population group they will be used as each population can have its own unique presenting characteristics (Turner-Stokes 2000).

In addition to accurate assessment, subsequent optimal therapy management is then vital for children with ataxia following resection of posterior fossa tumour. In the next section the literature on physiotherapy management for children with ataxia will be introduced and the gap in literature acknowledged.

2.7 Evidence-based physiotherapy for children with ataxia

Multidisciplinary rehabilitation which crucially includes physiotherapy is the mainstay of management for children with ataxia, aiming to help children improve their mobility and functional ability and thus help them return to school and increase their participation in other activities. Considering the long-term nature of ataxia in children with posterior fossa tumours, and the high incidence of balance and co-ordination problems, it is important to consider what physiotherapy interventions are most effective, and how they can be best targeted for this patient group. Identification of what type of physiotherapy and how often this should be completed was raised as one of the main priorities by the Public and Patient Involvement (PPI) group involved with the CARS study which subsequently informed the planning of this programme of work.

Physiotherapy input for children with PFT

Specific to paediatric neuro-oncology, neuro-rehabilitation is recognised as essential (NICE 2014) with physiotherapy playing an integral part of a multi-disciplinary approach. The goal of rehabilitation is to assist the child to reach their optimal physical function and to help with reintegration into education and the community (Pruitt et al. 2011). There is low quality

evidence of the benefits of physiotherapy provided as part of an inpatient rehabilitation package (Philip et al. 1994, Bedell et al. 2008) but, as yet, there is no consensus regarding the most effective type, intensity or timing of intervention. A search for studies about physiotherapy management specifically for children with ataxia following surgical resection of brain tumour revealed no papers, highlighting the significant lack of literature in this area. Therefore, a broader literature search was undertaken to include ataxia from different pathologies to see what evidence could be translated across to the population under consideration in this thesis. The literature review for physiotherapy interventions for children with ataxia is presented in the next chapter.

2.8 Summary

Overall, the literature on ataxia and children with PFT demonstrates a small but emerging body of evidence highlighting the high incidence of ataxia in children with PFT. However, the natural history of ataxia using standardised outcome measures has not been described prior to the contribution of the CARS study. There is evolving literature on the use of ataxia rating scales in paediatrics which could be translated to children with PFT, yet to date, there is no information regarding sensitivity to change of these scales. There is a particular lack of literature about the effectiveness of physiotherapy interventions for children with ataxia following surgical resection of PFT despite physiotherapy being part of routine practice. The available evidence will be explored further and critically reviewed in the following literature review.

Chapter 3 – Literature review – Physiotherapy interventions for children with ataxia

In this chapter an overview of ataxia is presented with consideration of the existing evidence underpinning the effectiveness of physiotherapy in adults, whilst highlighting the gap in this area in children. Physiotherapy interventions will be described and defined before presenting a systematic review of the literature. The aim of the review was to map and critically evaluate the type, range, scope and scientific quality of exercise and physiotherapy interventions on impairment, function, participation and quality of life for children and young people with ataxia. The methods used within the systematic review are examined alongside the subsequent results, discussion and recommendations. This systematic review was published in 2019 (Hartley et al. 2019) (Appendix 3).

Despite physiotherapy (as part of a multidisciplinary therapy programme) being the predominant treatment for ataxia in children with posterior fossa tumours (PFT) there is a significant lack of literature about physiotherapy specific for this population. Initial searches demonstrated only one single case study describing the physiotherapy management of ataxia/co-ordination in a child following surgical resection of a PFT. Therefore, to further inform the planning of subsequent phases in the study, a systematic review was carried out to evaluate the effectiveness of rehabilitation/physiotherapy interventions for children with ataxia as their primary impairment and from any cause, to provide further information which may be useful to apply in the rehabilitation of children with PFT.

3.1 Introduction

Ataxia is an umbrella term for a cardinal group of symptoms, that could originate from three main impairments: of the cerebellum, of the peripheral nervous system and of the vestibular

apparatus known as cerebellar ataxia, sensory ataxia and vestibular ataxia respectively. Cerebellar ataxia is a common childhood movement disorder, with an estimated worldwide prevalence of 26/100,000 (Musselman et al. 2014). Cerebellar ataxia arises due to damage or dysfunction affecting the cerebellum and/or its input or output pathways (Marsden & Harris 2011). This systematic review focuses on cerebellar ataxia, hereafter referred to as ataxia.

Ataxia is typically used to describe coordination and balance problems. The primary features of ataxia include difficulty grading, timing, scaling and coordinating movement of the limbs, trunk, and eyes, as well as the muscles of the face, mouth and throat. These impairments may result in a range of functional difficulties involving balance and walking, reaching, grasping and manipulation, eye movement, swallowing, and speech intelligibility (Pavone et al. 2017).

Ataxia in childhood may be acquired (e.g. following stroke, traumatic brain injury (TBI), cerebral palsy (CP), or cerebellar tumour), inherited (e.g. Friedreich's ataxia (FRA)), or idiopathic (Mariotti et al. 2005). Due to the incidence of posterior fossa tumours in childhood, one of the most common causes of acquired/acute onset of ataxia in children is due to cerebellar tumour. Ataxia is caused by damage or dysfunction of the cerebellum and its associated connections (Manto 2002). Specifically, with respect to children with posterior fossa tumours, ataxia is thought to be due to damage to the deep cerebellar nuclei (Kuper et al. 2013). In the absence of effective pharmacological options, rehabilitation following PFT resection, particularly physiotherapy, remains the mainstay of treatment for children with ataxia. Indeed, for children with brain tumours, NICE quality standards for children and young people with cancer (2014) identify that children should have access to timely rehabilitation both as an inpatient and on discharge home. However, there is no specific guidance as to the type, intensity or duration of physiotherapy.

To date, eight literature reviews have reported on the effectiveness of rehabilitation for primarily adults with ataxia (Martin et al. 2009, Trujillo-Martin et al. 2009, Artigas et al. 2013, Martins et al. 2013, Fonteyn et al. 2014, Marquer et al. 2014, Synofzik & Ilg 2014 and Milne et al. 2017). These reviews have chiefly but not exclusively concentrated on physiotherapy and exercise interventions. A detailed analysis of the eight reviews was undertaken to examine whether children were included in this evidence base and to determine the need for a specific review of the literature concentrating on children. The results of this analysis indicated that none of the reviews comprehensively searched for studies that included children or clearly reported the effect of interventions on children.

Evidence about the efficacy of interventions based on studies primarily involving adults with ataxia will not necessarily translate to children and young people with ataxia for several reasons. Brain development continues throughout childhood as increasingly more sophisticated movement repertoires are acquired through experience-based learning (Johnson 2001). In particular it is thought that cerebellar growth and development reveals a delayed peak compared with the rest of the brain (Tiemeier et al. 2010). Normative data derived from the International Cooperative Ataxia Rating Scale (ICARS) (a scale which quantifies the level of ataxia impairment), has shown that typically developing children only approach their 'adult normative' score of zero (indicating no coordination problems) at approximately 12 years of age (Sival & Brunt 2009). Equally when using the shorter Scale for the Assessment and Rating of Ataxia (SARA) it has still been shown that children only approach the 'adult normative' overall score at 10 years of age, with children reaching their 'adult normative' in the gait and speech items quicker than with the limb kinetic tests (Brandsma et al. 2014). This finding could be explained by reports that growth of the anterior and superior posterior-cerebellar regions (which determine kinetic and executive functions) stabilises at 14 to 17 years of age, compared with growth of the cerebellar vermis that is reported to plateau at 8 years of age (Tiemeier et al. 2010). This is a significant consideration in terms of understanding the impact of age on both planning physiotherapy

interventions and the impact on assessment of ataxia, where it is important to note the natural age-related changes especially if a longitudinal study is undertaken.

Children's central nervous systems may therefore respond differently to rehabilitation interventions when compared to a mature but similarly impaired adult system. Age is likely to affect engagement and compliance with the chosen modality or intervention and may impact the targeting and timing of rehabilitation efforts. Children have different body configurations, and different information processing capacities compared to adults. They respond differently to motor learning and skill acquisition paradigms, suggesting that children may require more exercise practice time before learning is consolidated compared to adults (Sullivan et al. 2008). Certain cerebellar pathologies are more prevalent in children e.g. midline floor of the fourth ventricle tumours whereas many of the spinocerebellar ataxias (SCAs) emerge only in adulthood with progressive degeneration of predominantly Purkinje cells across cerebellar areas (Koeppen 2005). These different pathologies impact cerebellar function in different ways and may require different rehabilitation strategies. It seems likely that rehabilitation programmes for children with an acute condition with the potential to improve may require a different focus compared with management of adults with deteriorating progressive conditions. As none of the review authors searched specifically for studies with children, or focussed on, or reported interventions or outcomes for children and young people with ataxia, the overall picture of research in this population is not well understood. An up to date and comprehensive assessment of the evidence is required to develop a better understanding the effectiveness of exercise and physiotherapy interventions for children and young people with ataxia.

3.1.1 Physiotherapy and exercise interventions

Physiotherapy aims to restore movement and function following injury, illness or disability using movement, exercise, and manual therapy, as well as education and advice (CSP 2013). Physiotherapy may include exercises as described below, and/or task specific

training with the aim of (re)acquiring a motor skill; exercises that focus on regaining or sustaining control of the proximal muscles of the trunk, shoulder and pelvic girdle; exercises that aim to improve static and dynamic balance, and proprioception as a component of postural control; and stretching exercises that aim to improve range of movement. Adjuncts such as treadmill training with or without partial body weight support, functional electrical stimulation of voluntary muscles, training with robotic exoskeletons and 'exergames' that use computer technologies to provide an interactive environment that requires limb movement to react to on screen game play (e.g. Wii, Xbox), may also be included as part of a physical therapy training programme (Ryan et al 2017, Ataxia UK 2016, Hickman et al 2017).

Exercise is defined as:

> 'physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective' (Caspersen et al. 1985, p128).

Exercise may improve the following components of physical fitness: muscle strength, muscle endurance, and cardiorespiratory fitness. Exercise interventions may be categorised as resistance training or aerobic (endurance) training based on the component of fitness the exercise programme is targeting. Resistance (strength) training is defined as the body's muscles working or holding against an applied force. Body weight, free weights, machine weights, and elastic bands may be used to apply force (USDHSS 2018). Aerobic training comprises the body's large muscle groups moving in a rhythmic manner over a sustained period of time (USDHSS 2018). Examples of aerobic exercise include walking, running, cycling, and arm ergometry. Endurance training or cardiovascular training is a type of aerobic training that includes activities that increase breathing and heart rate. Exercise programmes may target muscle strength, muscle endurance or cardiorespiratory fitness, or a combination of these components described as 'mixed training' (Ryan et al. 2017).

3.1.2 Neuroscientific and theoretical foundations for interventions

Physiotherapy interventions for people with neurological conditions are informed by a broad understanding of neuroanatomy, neuropathology, neurophysiology, and neuroplasticity, as well as the application of motor learning (change within the central nervous system (CNS) in response to practising a skill) (Krakauer 2006) and skill reacquisition principles. These principles can inform the selection of type and intensity of treatment and are considered in conjunction with an understanding of the impact of damage to the specific area involved with the child's pathology. The function, role and potential recovery of the cerebellum is also relevant when considering the development of physiotherapy interventions to improve function in children with ataxia. The cerebellum provides continuously adapted information for balance control and decision-making regarding speed, force and direction of intended movements (Lawerman 2018). Additionally, the cerebellum plays a key role in motor learning (Manto et al. 2012, Hardwick et al. 2013), for this reason it was customary to believe that interventions to improve motor function for people with ataxia would be ineffective (Kabat 1955). Recent evidence suggests that although adaptive learning is affected by cerebellar damage (Konczak & Timmann 2007) motor learning is possible despite cerebellar pathology, though potentially at a slower rate (Berger et al. 2005, Therrien et al. 2016). In fact, Therrien et al. (2016) have shown that people with cerebellar dysfunction can use reinforcement learning to learn and retain new skills and have subsequently argued that cerebellar impairment may indirectly disrupt reinforcement learning but does not interfere with the underlying reinforcement mechanism. Sparing of the deep cerebellar nuclei and the extracerebellar systems is thought to be a factor in recovery of motor function in children following cerebellar injury (Konczak & Timmann 2007). Motor learning specific to cerebellum damage is discussed further later in the thesis when considering intervention choice for Phase 4 of this programme of work.

Contemporary rehabilitation approaches for people with cerebellar dysfunction may involve strategies that compensate for the underlying impairment e.g. increasing inertia by

weighting equipment such as walking aids, or weighting the ataxic limb, or strategies that aim to improve or restore function by treating cerebellar-specific impairments, e.g. through balance and ocular training (Marsden & Harris 2011). Restorative interventions are thought to improve impairment of function and to work directly on modifying the underlying neural mechanisms, whereas compensatory interventions provide an alternative strategy to perform the same task (Pomeroy et al. 2011). The potential mechanisms underlying the restorative and compensatory approaches are the subject of ongoing investigations (e.g. Bhanpuri et al. 2014). It is also possible that exercise interventions, as defined above, may increase physical fitness and physical activity levels and deliver health promoting effects. Exercise interventions may also confer benefits that reside outside the biomedical sphere by having a positive effect on a child's well-being and life experience. These broader outcomes are considered essential to understanding childhood disability and should be incorporated in research protocols (Rosenbaum & Gorter 2012).

3.2 Methods

3.2.1 Aims

The aims of this systematic review were to map and critically evaluate the type, range, scope, and scientific quality of exercise and physical therapy interventions on impairment, function, participation, and quality of life for children and young people with ataxia.

3.2.2. Systematic review approach

A systematic review methodology guided by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2019) was undertaken but adapted in consideration of the anticipated lack of RCTs to include other trial designs (Higgins et al. 2019).

Criteria for considering studies for this review

The PICO framework (population, intervention, comparisons and outcomes) (Sayers 2008) was used to develop the literature search strategy and is summarised in Table 3.2. Further

detail about the population, interventions, comparisons and outcomes is presented in the following sections.

Table 3.2 PICO search strategy (summary)

Population	Children and young people 18 years old or under, of any functional ability, with cerebellar ataxia as the primary impairment.
Interventions	Physical therapy interventions or exercise interventions to improve one of the components of physical fitness, or co-ordination, dexterity, balance, posture or function.
Comparison	Exercise and physical therapy interventions versus no treatment, or usual care, or a comparison of one exercise or physical therapy intervention with another exercise or physical therapy intervention (where study design permitted).
Outcome	Activity, participation, health related quality of life, incidence and nature of adverse events. Secondary outcomes related to body functions and structures (WHO 2001).

3.2.2 Types of studies

All prospective and retrospective intervention studies where before and after outcome data were collected, such as randomised controlled trials, quasi-randomised controlled trials, non-randomised studies, and single case experimental designs were included. Case studies were included if measures of outcome were reported. Case reports and case descriptions where the impact of an intervention was not determined, and where no measures of outcome were reported, were excluded from the review.

Participants

Studies that included children and young people 18 years old or under, of any functional ability, with ataxia as the primary impairment were eligible. Studies that included both participants who were under 18 years and those over 18 years of age were categorised as having a mixed aged group and were included in the review but reported separately. If data from participants 18 years old or under could be extracted from studies with mixed age groups, these data were reported separately.

Participants with ataxia as a result of posterior fossa tumour, stroke, cerebral palsy (CP), brain injury, idiopathic cerebellar ataxia, autosomal recessive ataxia (e.g. FRA; early onset ataxia such as ataxia telangiectasia (AT); adolescent onset ataxia) or autosomal dominant ataxia were included. Studies where participants had other childhood conditions, where ataxia is a feature but is not the primary motor impairment (e.g. Angelman syndrome, Wilson's disease) were excluded. Participants with other conditions known to affect the cerebellum but with other primary signs and symptoms, such as developmental coordination disorder, and autism, were also excluded. Studies that included participants with ataxia as a result of self-limiting conditions that usually resolve (e.g. some types of acute neurotoxicity or infection) were excluded.

3.2.2 Types of interventions

Studies using or describing the following exercise, training and physical therapy interventions were included if they addressed:

a) Exercise interventions that aimed to improve one of the components of physical fitness i.e. muscle strength, and/or muscle endurance and/or cardiorespiratory fitness, including e.g. resistance training and/or aerobic training exercises.
b) Physical therapy interventions that aimed to improve co-ordination, and/or dexterity, and/or balance, and/or posture.
c) Exercise interventions or physical therapy interventions that used exercise devices such as treadmills, body weight support systems, and robot assisted exercise protocols to improve a component of physical fitness and/or co-ordination, and/or dexterity, and/or balance, and/or posture.
d) Exercise interventions or physical therapy interventions that involved riding horses or mechanical horses, exercises in water, including swimming, to improve a component of physical fitness and/or co-ordination, and/or dexterity, and/or balance, and/or posture.
e) Physical therapy interventions that aimed to improve physical functioning through task or part-task specific practice e.g. constraint induced movement therapy (CIMT).

f) Physical therapy interventions described as ‘Bobath’ or neurodevelopmental therapy (NDT).

g) Functional electrical stimulation (FES) and/or neuromuscular electrical stimulation (NMES) and functional orthoses such as Lycra garments, and upper and lower limb splints, were only included if the intervention was used in conjunction with exercise interventions or physical therapy interventions (reflecting conventional practice) or as a comparison to exercise interventions, as defined above, to improve one of the components of physical fitness, or co-ordination, dexterity, balance, posture or function.

The following interventions were excluded because they were not considered to be exercise or physical therapy interventions as defined in the protocol; psychological interventions, interventions restricted to improving communication (speech or other means of communication) or swallowing, breathing exercises, acupuncture, vibration therapy, or types of non-invasive brain stimulation (in isolation or combined with exercise interventions). Comparisons of interest (where study design permitted) were exercise and physical therapy interventions (as described above) versus no treatment, or usual care, or a comparison of one exercise or physical therapy intervention with another exercise or physical therapy intervention.

3.2.3 Outcome measures

As there are no gold standard outcome measures for children with ataxia, the following outcomes were indicative but not specified as inclusion criteria for this review.

Primary outcomes

1. Activity defined as a person's ability to execute a task (WHO 2001). Primary outcomes may focus on completing activities of daily living and application of skills within a range of different settings (e.g. the community / home / school / primary or secondary care setting).
2. Participation defined as a person's involvement in a life situation (WHO 2001).

3. Health Related Quality of Life (HRQoL) defined as the impact of disease and treatment on physical, psychological, and social domains of health as distinct areas that are influenced by a person's experience, beliefs, expectations and perceptions (Testa & Simonson 1996, Solans et al. 2008).
4. The incidence and nature of adverse events such as injury, and delayed onset muscle soreness, where reported.

Secondary outcomes

1. Body functions and body structures defined as changes in physiological systems or in anatomical structures (WHO 2001) e.g., muscle strength, endurance, fatigue, pain, cardiorespiratory fitness, balance, ataxia severity, and coordination.

Any measure that purported to measure these outcomes was included, regardless of whether or not it was validated specifically for children with ataxia.

Outcomes were collected for the following time points: short term (0 to 1-month post-intervention), intermediate term (>1 month to 6 months post-intervention), and long term (> 6 months post-intervention).

3.2.4 Search methods for identification of studies

The following databases were searched from inception to February 2018; Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), CINAHL (EBSCOhost), ClinicalTrials.gov, EMBASE (OVID), Ovid MEDLINE, Physiotherapy Evidence Database (PEDro), and Web of Science (all databases). The conference proceedings of the International Society for Paediatric Oncology (SIOP), the International Symposium on Pediatric Neuro-oncology (ISPNO) (2005-current) and World Confederation for Physical Therapy (WCPT).

Table 3.3 Literature review search terms

Population
child* OR pediatric OR paediatric OR adolescent OR infant
Impairment
ataxi* OR atax* OR co-ordination OR “motor impairment” OR “balance impairment” OR “postural instability
Intervention
“physical therapy” OR “physiotherapy” OR “rehabilitation” OR exercise OR “exercise therapy” OR “physical activity” OR “home exercise programme” OR “balance training” OR “postural training” OR “co-ordinative training” OR “hydrotherapy” OR “aquatic therapy” OR “neurodevelopmental therapy” OR “strength training” OR “muscle strengthening” OR “virtual training” OR “treadmill training” OR “kinesiology taping” OR “lycra” OR “FES” OR “functional electrical stimulation” OR “neuromuscular electrical stimulation” OR “NMES”.
Outcome*
*As stated above studies were not selected based on outcome measure. Outcome measures were indicative only in order not to limit numbers of studies, therefore outcome was not included in the search terms.

This search strategy was adapted as appropriate for each source. Limits were not imposed on searches for language, date, or publication status. The reference lists of included studies and relevant systematic reviews identified with the search results were also searched.

3.2.5 Selection of studies

Two people (the researcher and a member of the supervisory team with expertise in conducting systematic reviews considering physiotherapy interventions) independently screened the titles and abstracts of the search results and excluded studies that did not meet the search criteria. Where studies appeared to meet the inclusion criteria, or where there was any doubt about inclusion, the full text of the published paper was retrieved. The same two people independently reviewed these papers against the inclusion criteria. Any disagreements regarding the exclusion of studies, at any stage of the review process, were resolved through discussion. Where an agreement about inclusion or exclusion could not be reached, another supervisor (with expertise in conducting reviews on management of ataxia) made the final decision.

3.2.6 Data extraction and management

Two people (as stated above the research and supervisor with expertise in this area) extracted data independently. Disagreements about the extraction of data were resolved by discussion. If a resolution was not reached, another supervisor as detailed above was consulted. The following information was extracted, where possible:

- Authors, title, abstract, publication type, publication record, country of origin
- Study design
- Sample size
- Study population: sex, age, ethnicity, diagnosis, type of ataxia, and gross motor function, where sufficient information was provided. Walking function was recorded, where possible, as unaided walking, walking with aids, or unable to walk, and according to other validated measures e.g. Gillette Functional Assessment Questionnaire (Gorton et al. 2011). Ataxia severity was recorded where possible e.g. SARA (Schmitz-Hubsch et al. 2006), Brief Ataxia Rating Scale (BARS) (Schmahmann et al. 2009)
- Intervention: aim of the intervention, type of exercise programme (e.g. aerobic exercise), mode of delivery (e.g. home programme), type(s) of location(s) where the intervention occurred (including any necessary infrastructure or relevant features), supervised or unsupervised programme, exercise mode (e.g. cycle ergometry, treadmill), exercise dose (i.e. duration, intensity, and frequency of exercise), tailoring/modification of the intervention to an individual (what, why, when, how), duration of programme.
- Intervention provider: profession, expertise, background, specific training received.
- Compliance: fidelity (whether the intervention was delivered as intended) and adherence to the prescribed dose (frequency, intensity, duration); how and by whom this was assessed.
- Outcome measures.
- Results: short term (0 to 1-month post-intervention), intermediate (greater than 1 month to 6 months post-intervention), and long term (> 6 months post-intervention) follow-up.

- Adverse effects.
- Conflicts of interest, declarations of conflicts of interest, and sources of funding.

3.2.7 Study appraisal and data synthesis

The methodological quality of the included studies was appraised using checklist and appraisal tools relevant to the study design e.g. The Joanna Briggs Institute Checklist (2016) for case reports and case series, and the CONSORT agreement for n=1 trials (Shamseer et al 2016). The Oxford Centre for Evidence-Based Medicine (OCEBM) level of evidence classification (OCEBM 2011) (Table 3.4) was also used to classify study design. This classification method is consistent with other internationally recognised guides. Where disagreements could not be resolved through discussion between the researcher and supervisor a final decision was made by the second supervisor involved in the systematic review.

Table 3.4. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Level of Evidence	
Level 1*	Systematic review of randomised trials or *n*-of-1** trials
Level 2*	Randomised trial or observational study with dramatic effect* (*level may be graded down on the basis of study quality, imprecision, indirectness, etc.)
Level 3*	Non-randomised controlled cohort or follow up study
Level 4*	Case series, case control studies, or historically controlled studies.
Level 5	Mechanism based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size.

** Definition of *n*-of-1 trial: a variation of a randomized controlled trial in which a sequence of alternative treatment regimens is randomly allocated to a patient. The outcomes of regimens are compared, with the aim of deciding on the optimum regimen for the patient.

The data were synthesised using narrative synthesis grouped according to the intervention used in the study. The extracted data were also tabulated to allow comparison across studies enabling examination of PICO elements.

Where outcome measures and assessment time points were the same across studies (in this case only for Ilg et al (2012) and Schatton et al (2017)), meta-analysis was also then conducted to determine the effect of videogame training of SARA scores.

3.3 Results

3.3.1 Type, range, scope and methodological quality of selected studies

After the removal of duplicates, 1927 studies and 16 conference abstracts were screened. Following screening, 124 full text studies were assessed for eligibility. Of these, 56 were excluded as they did not involve children, 24 did not have ataxia as the primary diagnosis/presenting feature, and 22 did not meet the intervention criteria stated in the search strategy. Two studies could not be obtained (Cytowicz & Lodzinski 1973, Tauffkirchen 1970). This review was conducted in 2018[1] and included 20 studies (forming the basis of a published article, Hartley et al. 2019, Appendix 3). All studies were published in the 20 years prior to the search being conducted (1999-2018), ten in the five years prior to the search. The PRISMA flow diagram (Moher et al. 2009) is presented in Figure 3.1.

[1] Literature published after the literature search is examined in the discussion (Chapter 9).

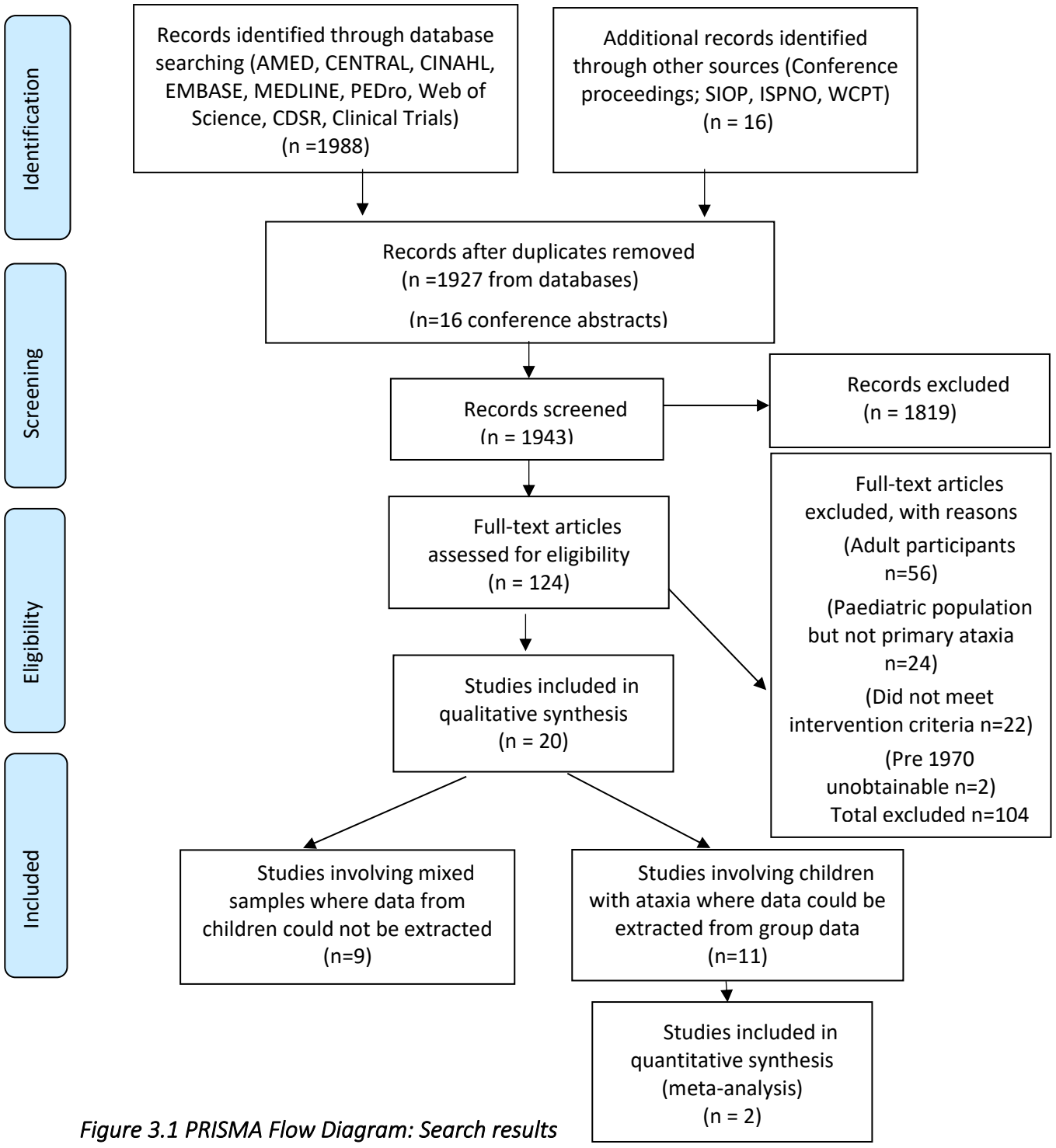


Figure 3.1 PRISMA Flow Diagram: Search results

A total of 40 children with ataxia as a primary impairment participated in the studies included in this review. The ages of the children with ataxia, where stated, ranged from 5 years to 18 years (median 13 years). The duration of the intervention, where stated, ranged from 2 weeks (Ada et al. 2009) to 19 months (Sartor-Glittenburg & Brickner 2014) (median 7 weeks), and, where stated, intensity ranged from 10 minutes per session (Ada et al. 2009)

to 2 hours per session (Bar-Haim et al. 2006), (median 45 minutes per session). Frequency ranged from once every three months (Harris-Love et al. 2004) to six days per week (Ada et al. 2009), median 3 sessions a week, excluding an outlier where Lycra garments were prescribed daily for six weeks, for 6 hours a day plus usual physical therapy care for 10-30 minutes per day (Nicholson et al. 2001).

3.3.2 Studies involving mixed groups where data from children with ataxia could not be extracted

Nine included studies recruited mixed groups of participants, either children with adults, or children with ataxia with children with other primary impairments. Data from the children with ataxia in these studies could not be extracted for this review. However, the studies are briefly discussed below, and an overview of the results is also presented in table format in Appendix 4.

Five studies with children with cerebral palsy, with sample sizes ranging from 8 to 70 participants, included one, (Bar-Haim et al. 2006, Blundell et al. 2003), two (Knox & Lloyd Evans 2002), three (Schroeder et al. 2014), or six (Van Hedel et al. 2016) participants with ataxia as their primary impairment. The study by Bar Haim et al. (2006) was judged at OCEBM level 3 for an RCT downgraded from level 2 due to increased risk of bias for being underpowered. The other four studies (Blundell et al. 2003, Knox & Lloyd Evans 2002, Schroeder et al. 2014 and Van Hedel et al. 2016) were all single group before and after studies and judged at OCEBM level 4. Interventions included neurodevelopmental therapy (NDT) vs Adeli Suit Treatment (training of gross motor function whilst wearing an externally fitted suit which provided stability and resistance) (Bar-Haim et al. 2006), strength training (Blundell et al. 2003), NDT (Knox & Lloyd Evans 2002), aerobic treadmill training (Schroeder et al. 2014), and robot assisted gait training (Van Hedel et al. 2016). Biffi et al. (2017) conducted an OCEBM level 4 before and after trial, to investigate the efficacy of an immersive virtual reality platform to enhance walking ability in children with acquired brain injury. One child with ataxia was included in a total sample of 12 children. Significant

improvements were reported in gross motor function, endurance (6MWT) and autonomy in daily life. Overall, small and predominantly short-term benefits were reported in this group of six studies that cannot be used to draw conclusions about the effectiveness of these interventions for participants with ataxia.

Of the remaining three studies in this group, Nardone et al. (2014) included one young person aged 16 in an otherwise adult sample of 27 participants with cerebellar dysfunction caused by either degenerative disease or cerebellar stroke, in an OCEBM level 4, single group (before and after) study. Small short-term positive effects in both groups were reported following a balance and gait training protocol. Sabel et al. (2016) conducted a randomised cross-over trial (downgraded from OCEBM level 2 to level 3 due to increased risk of bias for being underpowered) that compared active video-gaming and coaching with usual care in a group of 13 children following treatment for brain tumour. Three of the cohort had posterior fossa tumours although specific assessment of ataxia was not included. The results demonstrated that the home-based intervention was feasible and improvements in body coordination were reported. Santos et al. (2017) included one child aged 15 years in an otherwise adult group of 28 people with SCA in an OCEBM level 4 prospective (before and after) feasibility trial of virtual reality balance training. Improvements were reported in balance and quality of life. None of the data for the children with ataxia in these three studies were reported separately and therefore no conclusions could be drawn about the effectiveness of the intervention for these participants.

3.3.3. Studies involving children with ataxia whose data could be extracted

The remaining eleven studies (summarised in Table 3.5) involved children with ataxia whose data could be extracted for this review (Ada et al. (2009), Sartor-Glittenburg & Brickner (2014), Harris-Lover et al. (2004), Nicholson et al. (2001), Mulligan et al. (1999), Cernak et al. (2008), Frank et al. (2011), Ilg et al. (2012), Synofzik et al. (2013), Da Silva and Iwabe-Marchese (2015) and Schatton et el (2017). Schatton et al. (2017) included data

from one participant previously reported in the n=1 pilot study conducted by Synofzik et al. (2013). In the following summary, data from this child have only been counted once. The studies included here were conducted mainly in North America (n=4), with additional contributions from Australia, Brazil, Germany, New Zealand, and the United Kingdom. This group of studies included a total of 21 children, aged 5 to 18 years; eleven boys and nine girls (one paper did not state gender) with progressive ataxia (n=14), ataxic CP (n=3), cerebellar/brain stem infarct (n=1), traumatic brain injury (n=1), cerebellar tumour (n=1) or a non-progressive cerebellar ataxia (n=1).

Five studies provided balance, coordination or dexterity training; (Ada et al. 2009, Ilg et al. 2012, Synofzik et al. 2013, Da Silva and Iwabe-Marchese 2015, Schatton et al. 2017), three provided mixed training, classified as conventional physical therapy (Sartor-Glittenburg & Brickner 2014, Harris-Love et al. 2004, Mulligan et al. 1999), one study provided aerobic treadmill training (Cernak et al. 2008), one provided horse-riding training (Frank et al. 2011), and one provided a full body Lycra suit in addition to usual care (Nicholson et el 2001).

The duration of the interventions ranged from 2 weeks (Ada et al. 2009) to 19 months (Sartor-Glittenburg & Brickner 2014) (median 12 weeks). Where stated, intensity ranged from 10 minutes per session (Ada et al. 2009) to 60 minutes per session (Harris-Love et al. 2004) (median 37.5 minutes per session). Frequency ranged from once every three months (Harris-Love et al. 2004) to six days per week (Ada et al. 2009), median 3 sessions a week, excluding Nicholson et al. (2001) where Lycra garments were prescribed daily for six weeks, for 6 hours a day plus usual physical therapy care for 10-30 minutes per day.

Nine of these studies were judged as OCEBM level 4 evidence; these were five single case reports (Harris-Love et al. 2004, Cernak et al. 2008, Frank et al. 2011, Synofizik et al. 2013, Da Silva & Iwabe-Marchese 2015), one case series (Sartor-Glittenburg & Brickner 2014), two single case experimental designs (Ada et al. 2009, Mulligan et al. 1999) and one single group (before and after) design (Nicholson et al. 2001). Two before and after studies with

intra-individual comparison, blind assessment and extended baselines were elevated to OCEBM Level 3 evidence (Ilg et al. 2012, Schatton et al. 2017).

Table 3.5 Data extraction for the eleven main studies

Study	Study Design	Participants				Intervention			Outcome Measures	Results Short term (ST) Intermediate term (IT) Long term (LT)	Compliance (fidelity and adherence)	Adverse effects	OCEBM
		Age/ Sex	Size	Diagnosis	Functional Level	Description	Dose: duration, frequency, intensity	Provider/ Setting					
Ada et al. 2009 Australia	SCED (ABA design)	5 yrs, female	N=1	Cerebellar tumour (low grade) resected 3.5 years previously.	Reported UL coordination problems.	Dexterity training using a computerised tracking task on a computer.	2/52, 12 sessions, 10'	Home, supervised by parents.	Finger to nose test, 9HPT.	ST: 8% improvement in tracking. FNT and 9HPT improved but not significantly. IT and LT not reported.	Reported good adherence to the intervention.	Reported as not harmful.	4
Cernak et al. 2008 USA	Case Report	13 yrs, female	N=1	Cerebellar ataxia post brain haemorrhage (16/12 previous).	Non-ambulatory.	Partial body weight support treadmill training with over-ground practice.	4/52, 5x/wk,40'. Gap of 1/12 Then 4/12, 5x/wk, 30'.	PT dept and home-based training (with rehab assistant).	Gillette, Functional Walking Scale, WeeFIM (transfers and mobility subscale), number of unassisted steps.	**ST:** Minimal change at 1/12. **IT**: At 6/12 Gillette improved to walking for household distances. Transfers improved from moderate assistance to modified independence. Walking improved from maximum assistance to supervision. No. of unassisted steps improved from 0-200 LT not reported.	19/20 sessions completed in clinic. Not reported for home training.	Fatigue and discomfort from harness.	4
Da Silva and Iwabe-Marchese 2015 Brazil	Case Report	12 yrs, male	N=1	Ataxic CP	GMFCS level II	Video gaming targeted at balance using the Wii (with balance board).	4/12, 3x/wk 30'. Total 40 sessions	Not reported. Setting unclear.	GMFM-66, BBS, gait kinematics.	**ST**: BBS increased from 48 to 53 points, GMFM: no change in dimensions A-C; D increased from 64.63 to 65.33, dimension E increased from 72.63 to 81.98, the overall mean score improved from 71.69	Not reported.	Not reported.	4

										to 77.46. Gait parameters: no change reported. IT and LT not reported.			
Frank et al. 2011 USA	Case report	6 yrs, female	N=1	Ataxic cerebral palsy	Ambulatory GMFCS level 1.	Hippotherapy.	8/52, 2x/wk, 45' (16 Rx sessions).	PT delivered Rx at the stables.	GMFM-66, PODCI, PSPCSAYC.	**ST**: GMFM 66, Dimension D: no change (95) Dimension E improved from 87.5 to 93. PODCI improved significantly in 3 domains. PSPCSAYC scores on 2 of 4 domains improved by 2 points. **IT**: GMFM 66 D improved to 97.4, E improved to 94.4. PODCI improvement in 3 domains. PSPCSAYC minimal change. LT not reported.	Number of sessions reported. HEP adherence reported.	Not reported.	4
Harris-Love et al. 2004 USA	Case report	14 yrs, female	N=1	FRA	Walking frame and powered wheel chair for mobility. Assistance of 1 to stand.	PT and adapted PE inc; bimanual task, task orientated training, strengthening, stretching, gait training using a walking aid.	1x/month, 60' (school) for 12/12, plus x1 / quarter 60' (PT dept), plus 20-30' daily adapted PE, plus HEP, 5x/wk.	PT dept, school and home.	9HPT, SLST, manual muscle testing, passive ROM, gait speed, DLST, step length asymmetry, step time asymmetry, self-report falls history.	**ST**: at 12/12 9HPT reduced (60.0 to 56.6s). ROM static or improved. MMT declined SLST increased 2.7 to 2.9. Fall rate decreased (12 to 3.) Gait speed varied depending on walker type. IT and LT not reported.	Not reported.	Not reported.	4
Ilg et al. 2012 Germany	Before/ after,	11-20 yrs. N=10,	N=7/ 10≤ 18	Children with spinocerebellar ataxia. 2-17	SARA score 7-13.5	X Box coordinative training.	2/52, 4x/wk 60'.	Lab based training supervised,	SARA, Dynamic Gait Index	**ST**: significant improvement in	Noted training intensity	Not reported	3

	no control group (intra-individual control design)	male n=5, female n=5.	years old	years post diagnosis			Then 6/52, varied intensity; 20'-175'per wk.	followed by home based training.	(DGI), motion analysis (leg placement), ABC Scale (balance confidence) Measured at baseline, pre-treatment, post 2 weeks lab training, post 6 weeks home training.	SARA (-2 average) and DGI. Improvements in lateral sway and error during leg placement task. Non-significant improvements reported in ABC. IT and LT not reported.	correlated with improvement in SARA posture subscore.		
Mulligan et al. 1999 New Zealand	SCED (noted second intervention shorter) (ABCB design)	9 yrs (Male/female not reported)	N=1	Non-progressive congenital ataxia.	Able to climb stairs without a rail. Modified TUGG (from the floor) at first assessment: 72s.	Compared two PT interventions: Rx 1 - strengthening pelvic/trunk musculature and practising midline in sitting and kneeling. Rx 2 - challenge postural control in different positions with head mvts performed simultaneously to reduce amount of visual information.	11/52, 3x/wk, 30' gap 5/52. Then 5/52, 3x/wk 30'	Rx 1: PT in school Rx 2: researcher, setting unclear.	Modified TUGG GMFM, GMPM, timed independent stair climbing.	ST: mTUGG improvement of 35s (from first intervention to 5/52 post end of 2nd intervention). GMFM overall improvement from 81% to 96% at end Rx 2. GMPM not clearly reported (graph compared to reported results). Timed stair climbing improvements reported with and without a rail. Reported better maintenance of results at end of second treatment block. LT not reported.	Not reported.	Not reported.	4
Nicholson et al. 2001 UK	Before/ after (measures	2-17 yrs, N=12:	N=1/12	CP	Upper limb	Lycra garment – (continued to receive usual	2 weeks initial gradual exposure, then	Mostly home setting (not supervised).	PEDI, reach and grasp	**ST:** improvements in PEDI self-care +8, mobility +4, social	Group but not individual	Impaired functional	4

	on single occasion)	male n=7; female n=5.	child with ataxia.		impairment	therapy during study period).	6 hours per day for 6/52.		(motion analysis), self-devised parent questionnaire re practicalities of the Lycra garment.	domains +7. No change in PEDI care giver assistance score. Improved trunk stability and upper limb function reported. Parental questionnaire not reported. IT and LT not reported.	daily use of the garment reported.	mobility, discomfort. Found uncomfortable to crawl in suit.	
Sartor-Glittenberg and Brickner 2014 USA	Retrospective case report	16-22 yrs. N=3; one 16 yrs with ataxia.	N=1 with ataxia	TBI (5/12 post).	Walked with a walking frame and maximum assistance of 2.	Mixed group PT and individual Rx. Activities to improve proximal stability, coordination and balance. Outpatient day programme. Also included climbing on an artificial wall in rock climbing gym.	77/52, 4-5x/wk, weaned down to 1-2x wk.	Supervised with PT.	Muscle strength (0-5 scale), coordination (timed heel to shin, toe taps), BBS, SLST, FES, 6MWT, participation in activities via interview and observation.	**ST**: Increased lower limb strength, improved co-ordination in both LEs, BBS improved from 4 to 23, SLST improved from 0s to 3.5s (R), 0s to 1.5s (L), FES improved from 37 to 95, 6MWT improved from 61m to 259m. IT and LT not reported.	Not reported re therapy sessions, diary to HEP completed.	Not reported.	4
Schatton et al. 2017 Germany	Before/after, no control group (intra-individual control design)	6-29 yrs. N=10. male n=7, female n=3.	N=6/10 ≤18 years old	Children with SCA	SARA score 13-29	Exergame training. (Nintendo Wii® and Microsoft Xbox Kinect®)	Phase1; 1/52 lab, 4 x 60min session then 5/52 at home. Phase2; 2/7 booster then 5/52 home training x3 wk 45 min per session	Lab based training supervised, followed by home based training.	SARA, GAS, Romberg sitting task. Measured at baseline, pre-treatment, after phase 1, after phase 2.	**ST**: significant improvement in SARA (-2.5 average). Higher GAS. Reduced body sway. IT and LT not reported.	Noted training intensity at home correlated with improvement in SARA.	Not reported.	3

Synofzik et al. 2013 Germany	Case Report	10 yrs, male	N=1	AT diagnosed at 3 years old	SARA score gait 7/8 (severe ataxia)	Video gaming coordinative training.	1/52 clinic, frequency and intensity not stated 2 update sessions. Then 5/52 home. Update then 6/52 home.	PT (lab based) and home based	SARA, GAS, sway in sitting.	**ST**: no change between 2 baseline phases. End of intervention SARA improvement of 4 points. GAS standing +2, sitting +1. Mvt analysis: less sway in sitting 2nd baseline to end of intervention. IT and LT not reported.	Not reported.	Not reported.	4

Abbreviations not appearing elsewhere: PE = physical education, HEP = home exercise programme, /52 = per week, /12 = per month, Mvt = movement, Rx = treatment, SLST = single leg stance test, FES = falls efficacy scale, DLST = double limb support time, LE = lower extremity, SCA = spinocerebellar ataxia, UE = upper extremity, Wk = week, AT = ataxia telangiectasia. ***See Table 3.4 for OCEBM levels**

The Joanna Briggs Institute Checklist (2016) for case reports was used to evaluate the quality of the case reports and the case series (n=6). The two single case experimental designs (SCEDs) were evaluated using the CONSORT agreement for the reporting of n=1 trials (Shamseer et al. 2016). Studies categorised as before and after trials (n=3) were evaluated using the NIH quality assessment tool (2014) for before-after (pre-post) studies with no control group. The separate evaluation of the methodological quality of these eleven studies identified comparable strengths and limitations. For this reason, the results of the critical appraisal of this group of studies were considered together.

Characteristics such as age, gender, diagnosis and genetic details (where relevant) were consistently reported but varied in the amount of detail offered. Psychosocial details were provided in one study (Sartor-Glittenburg & Brickner 2014). Imaging results were reported by Sartor-Glittenberg and Brickner (2014) and in supplemental information by Synofzik et al. (2013). Ataxia severity was rarely described in detail and only measured using a specific ataxia scale (SARA) in three studies from the same research laboratory (Ilg et al. 2012, Synofzik et al. 2013, Schatton et al. 2017). Gross functional capacity was classified in four studies using the Gross Motor Function Classification System GMFCS (Frank et al. 2011, Da Silva and Iwabe-Marchese 2015), or the Gillette Functional Walking Scale and WeeFIM (Cernak et al. 2008), or the PEDI (Nicholson et al. 2001). Walking ability was described but not consistently measured in all relevant studies. Interventions were well described, and the duration, frequency and intensity (dose) were consistently reported across all studies. Decisions about the prescribed dose of the intervention were not justified with respect to relevant theories or the results of other studies. Compliance was not consistently reported, particularly for home-based exercise programmes. Three studies identified primary outcomes (Cernak et al. 2008, Ilg et al. 2012, Schatton et al. 2017). Five studies reported measurement properties (validity and reliability) for one or more outcomes (Sartor-Glittenburg & Brickner 2014, Nicholson et al. 2001, Mulligan et al. 1999, Cernak et al. 2008, Frank et al. 2011). Only one study measured participation and quality of life outcomes

(Frank et al. 2011). All studies reported short-term outcomes (0-1 month post intervention). No long-term outcomes were reported. Assessor blinding was reported in four studies (Ada et al. 2009, Ilg et al. 2012, Synofzik et al. 2013, Schatton et al. 2017). Adverse events were not routinely reported. One study reported that the intervention was not harmful (Ada et al. 2009), and one study clearly reported harmful effects (Nicholson et al. 2001). None of the included studies reported involving children and/or parents in the design or evaluation of the intervention.

Effectiveness of the interventions

In the following evaluation minimal detectable change (MDC) and minimally clinically important difference (MCID) scores have been provided where available to facilitate judgement of the reported effectiveness of interventions. Where paediatric data are not available adult data have been used to provide proxy comparisons.

Conventional physiotherapy

Three papers reported the effects of conventional physiotherapy. Harris-Love et al. (2004) used bimanual task practice, task orientated training, stretching, strengthening and gait training using walking aids with a 14-year-old child with FRA. The intervention was provided once every three months over a twelve-month period (60 minutes per visit) and continued as a home exercise programme five times a week. Monthly school-based physiotherapy continued (60 minutes per session) plus school based physical education (20-30 minutes per session, up to five times per week). The additional intervention equated to an extra four hours of hospital-based physiotherapy plus the home exercise programme, five times per week over a 12-month period. The improvement of 3.4s on the 9-hole peg test (9HPT) was not considered clinically meaningful, however a reduction in the number of falls from 12 to 3 falls per month (self-report) in the context of a measured deterioration in areas such as strength, and gait speed, may be considered a clinically significant change for a child living with a progressive condition.

Mulligan et al. (1999) used a SCED (ABCB) with a child with non-progressive congenital ataxia (severity not reported), comparing strengthening and balance training (30 minutes, three times a week for eleven weeks) with interventions aimed to challenge postural control (30 minutes, 3 times a week for five weeks). Improvements were reported in the modified Timed Get Up and Go (TUG), Gross Motor Function Measure (GMFM), stair climbing, and the Gross Motor Performance Measure. However, it was difficult to evaluate the separate effects of each intervention as multiple measures were not undertaken in each phase, standard SCED statistical analysis was not used, and trends could be observed in the data from the A phase into the other phases.

Sartor-Glittenburg and Brickner (2014) reported a retrospective case report of a 16-year-old boy in the subacute phase following TBI. Ataxia severity was not measured but was reported as severe. He required a walking frame and maximum assistance from two people to walk short distances. A wide range of interventions were provided during 187 therapy sessions over 19 months. Improvements were reported for all outcomes. An improvement of 19 points in the Berg Balance Scale (BBS) exceeded the MDC of 5 points relevant for older adult clinical populations with an initial score of 0-24 points (Donoghue & Stokes 2009). An improvement of 198m in the Six Minute Walk Test (6MWT) exceeded the MCID reported as relevant for adults with a range of medical conditions (Bohannon & Crouch 2017). Motor co-ordination improved but did not reach age equivalent norms.

Video gaming and computer assisted training for dexterity/coordination, and balance

Five studies reported a positive effect of video gaming or computer assisted training in children/young people with ataxia. As the participant in Synofzik et al. (2013) was included in the data presented in Schatton et al. (2017), only data from this second study are presented in this summary. Ada et al. (2009) reported short-term but not statistically significant improvements in elbow dexterity (finger-nose test) and a timed upper limb task (9HPT) following a 2-week home programme of dexterity training for ten minutes per day, using a computer assisted elbow tracking task (gravity eliminated), with a 5-year-old girl

described as having severe upper limb ataxia following resection of a posterior fossa tumour. Da Silva and Iwabe-Marchese (2015) reported immediate improvements following a 4-month programme of video game balance training (Nintendo Wii), in addition to usual care, for a 12-year-old boy with ataxic CP (GMFCS II – able to walk in most settings). A six-point improvement was reported in the GMFM-66 (exceeding the MCID for a large effect size reported by Oeffinger et al. (2008), and a five-point improvement in BBS (exceeding an MDC of four points relevant for older adults with an initial score of 45-56 points (Donoghue & Stokes 2009). No improvement in gait kinematics was reported.

Ilg et al. (2012) conducted an intra-individual control study using an eight-week video co-ordination-game training (Xbox Kinect) programme (2 weeks in clinic (four 1-hour training sessions) followed by 6 weeks at home) with 10 children and young adults (*n*=7 ≤18 years old) with an inherited progressive ataxia as their primary impairment (mean SARA 10.9, range 7-13.5). A mean group change reflecting a 2-point improvement in SARA (more than one-point change would be considered a MCID for adults with a progressive ataxia (Schmitz-Hubsch et al. 2010)) and improvements in sway and leg placement were reported. Schatton et al. (2017) reported a mean 2.5-point improvement in SARA scores (exceeding the one-point MCID SARA change considered relevant for adults with a progressive ataxia (Schmitz-Hubsch et al. 2010). This was achieved at the end of a 12-week (1 week in clinic, 5 weeks at home, two update sessions and a further 5 weeks at home) video gaming programme (Nintendo Wii) using whole body controlled commercially available games for ten participants (*n*=6 ≤18 years old) described as having advanced SCA.

As Ilg et al. (2012) and Schatton et al. (2017) used SARA as their primary outcome measure and provided data for all participants at all time points, data from these higher quality studies were pooled to conduct a meta-analysis of the effect of videogame training on SARA scores. A comparison of change in SARA scores across time irrespective of age indicated a statistically significant and clinically meaningful reduction (improvement) in SARA scores

from baseline to the end of the intervention (median reduction of 2 points, $p<0.001$) as illustrated in Table 3.6.

A comparison of training time (overall dose) indicated that participants in the Schatton et al. (2017) study spent a median of 160 minutes training compared to those in Ilg et al. (2012) who spent a median of 70 minutes training (Table 3.7). This difference was statistically significant ($p=0.03$) but the increased dose does not appear to have made a difference to outcome as measured by SARA, suggesting that optimal dosages are yet to be determined.

A comparison of change across time by age using pooled data from 13 children (≤18 years old) with pooled data from seven adults indicated that although SARA scores for children improved by a median of 0.5 points more than adults, the difference was not statistically significant, ($p=0.49$) (Table 3.8). Adults in these studies completed a median of 18 extra minutes of training compared to children but the difference in training time was not statistically significant ($p=0.49$) (Table 3.9). (Although caution should be applied in interpreting these results as the studies were not powered to detect differences.)

Table 3.6 Comparison of change across time irrespective of age (n=20)

	Time point 1	Time point 2	Significance
SARA median change over time (IQR)	13.5 (9.5)	11.5 (8.3)	P<0.001[1]

[1]Wilcoxon signed rank test, IRQ = interquartile range

Table 3.7 Comparison of training time irrespective of age

	Schatton et al. 2017	Ilg et al. 2012	Significance
N	10	10	
Median time (IQR)	159.9 (23.3)	70.5 (110.5)	P=0.03[2]

[2]Mann-Whitney U test, IRQ = interquartile range

Table 3.8 Comparison of change across time by age

	18 yrs and under	18 yrs and over	Significance
N	13	7	
SARA median change over time (IQR)	2 (2.8)	1.5 (1.0)	P=0.49[2]

[2]Mann-Whitney U test, IRQ = interquartile range

Table 3.9 Training time (minutes)

	18 yrs and under	18 yrs and over	Significance
N	13	7	
Median time (IQR)	132 (122.4)	150 (45.0)	P=0.49[2]

[2]Mann-Whitney U test, IRQ = interquartile range

Treadmill training

Cernak et al. (2008) conducted a single case study with a non-ambulatory 13-year-old girl with ataxia following a brain haemorrhage and reported functionally meaningful improvements in the Gillette Functional Walking Scale (improved from a score of two up to six reflecting an ability to now walk indoors) and the WeeFIM mobility and transfer subscales. The intervention consisted of partial body weight support treadmill training (in conjunction with over ground walking practice) completed initially in the clinic setting (five days a week for four weeks) and then continued daily at home for a further four months (five days a week).

Hippotherapy

Frank et al. (2011) reported short-term (eight weeks) and intermediate (two months) gains in GMFM dimensions D and E in a 6-year-old girl with mild ataxic cerebral palsy (GMFCS I – walks independently with limitations in speed, balance and coordination) following an eight-week course of hippotherapy (16 sessions). Gains in the GMFM and the PODCI for global function, sports and physical function, and upper extremity and physical function,

exceeded the MCID for large effect sizes as interpreted by Oeffinger et al. (2008). Adverse effects were not reported.

Lycra garments

Nicholson et al. (2001) conducted a before and after study to investigate the effectiveness of wearing a Lycra garment (seven days a week, for six hours, for six weeks) and usual care (physical therapy home programme) on impairment and activity limitations with twelve children with CP, one of whom had ataxia and whose results were reported separately. The Paediatric Evaluation of Disability Inventory (PEDI) score (activity and participation levels) for this eight-year-old boy improved in self-care (+8 points), mobility (+4 points) and social domains (+7 points) following completion of the intervention at six weeks. Improvements in proximal stability were reported but the child was unable to crawl while wearing the suit and found it uncomfortable. Improvements in the PEDI appear to be under the proposed MCID for the PEDI of an 11-point change in scaled score (Iyer et al. 2003) although it is not clear if scaled or raw scores are reported by Nicholson et al. (2001).

3.4 Discussion

The purpose of this systematic review was to evaluate the effectiveness of exercise and physical therapy interventions for children with ataxia. It also aimed to report the type, range, scope and scientific quality of relevant studies. Twenty studies involving 40 children with ataxia met the inclusion criteria. Nine studies included children with ataxia along with children with a number of other primary impairments/diagnoses or grouped children with adult participants. Data for the children with ataxia were unable to be extracted from these nine studies. The eleven remaining studies provided data from a total of 21 children with ataxia that could be extracted for this review. The results suggest that only a small number of studies involving a very small number of children with ataxia have been undertaken to investigate the effectiveness of exercise and physiotherapy interventions for this population. The lack of RCTs suggests that research for children with ataxia is less well developed than

that for adults. Given that ataxia is a common childhood movement disorder (Musselman et al. 2014), and exercise and physical therapy interventions are the mainstay of treatments available to these children (Ilg et al. 2014) this result may be considered surprising.

The group of eleven studies considered in the main results for this review were of low methodological quality, consisting principally of single case reports and SCEDs. Overall, inconsistent descriptions and measurement of ataxia, poor reporting of adverse events, lack of long-term follow up, and the significant heterogeneity demonstrated in the type of intervention, age range, functional capacity, outcome measures and the duration, frequency, intensity and setting of the intervention, limits the extent to which comparisons can be made across studies. Methodological and reporting limitations reduce the confidence with which conclusions can be drawn about the effectiveness of exercise and physical therapy interventions for children with ataxia. It was also observed that measures of fidelity were poorly reported thus making it difficult to understand if the interventions were practicable, acceptable to the children and their parents, and able to be followed as intended.

This systematic review has revealed that research about the effectiveness of physical therapy and exercise interventions for children with ataxia is in a very early phase of its development and currently offers inadequate guidance about the efficacy of exercise and physiotherapy interventions for children with ataxia. Nonetheless, the results of the studies reported here were on the whole promising and indicate that outcomes for this population have the potential to be improved through physiotherapy and exercise. However, no firm conclusions could be drawn, and no recommendations could be made based on the evidence reviewed. If the potential of these interventions is to be realised, stronger research designs that counter the limitations of the studies undertaken to date will be needed.

RCTs would make an important contribution to future research. However, recruitment issues and achieving relatively homogeneous samples may challenge the feasibility of

running studies of sufficient size. Multi-centre studies and international collaboration might be needed to make these large-scale trials feasible. As an important first step, feasibility trials should be conducted before running fully powered RCTs. This would ensure that all the parts that make up the trial, including recruitment, randomisation, outcome measurement, adherence and compliance proceed as intended (Abbott 2014) and are acceptable to the children and parents involved. Home-based training, e.g., is likely to form a significant component of exercise interventions for children with ataxia (Ilg et al. 2014). However, Maring et al. (2013) reported that although 73% of children with FRA were prescribed a home exercise programme, only 9% of these children carried out the programme as directed. An understanding of the acceptability of, and compliance with, interventions, over the short and long-term, are critical to the development of RCTs. Potential problems with these programme components could be ironed out not only through running feasibility studies, but also by involving children and parents in the design and planning of future studies and intervention programmes. SCEDs and *n*-of-1 trials, including prospective multiple cross-over and randomised case series designs, also offer valid alternatives to RCTs in situations challenged by heterogeneity and when large samples may be difficult to obtain (Vohra et al. 2015). Clear reporting of, e.g., randomisation, primary outcomes, adverse events and blinding of assessors should be included, and the CONSORT extension for reporting of *n*-of-1 trials (Joanna Briggs Institute Checklist 2016) should be followed.

Children with ataxia may respond differently to physiotherapy and exercise interventions when compared to children with other primary impairments (Ilg et al. 2014), and when compared to adults with ataxia (Ilg et al. 2012). Involving children with different primary impairments (ataxia, spasticity, athetosis) or combining the data of children and adults in the same study, evident in twelve of the twenty trials that met the inclusion criteria for this review, should be reconsidered unless the potential effectiveness of the proposed intervention can be justified for all participants. If combining children with different

pathologies and primary impairments in trials is considered a valid means of testing the efficacy of interventions, future studies should consider involving larger numbers of children with ataxia to enable subgroup analysis to be undertaken so that conclusions can be drawn about the impact of interventions for particular groups. Conducting separate studies for children with ataxia arising from a progressive condition to those for children with ataxia arising from a non-progressive form of ataxia seems reasonable, given the likely differing aims of the study, the different underlying pathological mechanisms that could affect the type of intervention used, and the expected direction and meaning of responses to interventions. For example, the response to exercise interventions may differ for children with malignant posterior fossa tumours depending on the degree of damage to the dentate nuclei and the inferior vermis (Puget et al. 2009). Children with conditions where lesions may be quite discrete are also likely to respond differently to exercise and physical therapy interventions when compared to children with more widespread involvement of the cerebellum, such as that found in progressive conditions (Ilg et al. 2012). These points not only stress the value of consistent and clear reporting of imaging results and lesion location in intervention studies, but also the importance of giving further consideration to the length of follow-up and justifying the recommended dose. Key morbidities e.g. such as visual and cognitive impairment, as well as measures of extracerebellar involvement (e.g. via the Inventory of Non-Ataxia Symptoms (Jacobi et al. 2013)), should also be reported to offer a more rounded account of a child's other impairments and a better understanding of the feasibility of delivering the intervention.

This review identified a diverse array of treatment interventions, with regards to the type, intensity, frequency, duration and setting. No justification was provided regarding decisions about dose. Although interventions are tailored according to individual need, these variations make it difficult to compare studies, to carry out meta-analyses, and to conduct replication studies. It is also difficult to examine the effect of usual care as well as other activities that children engage in as details are not always provided, and usual care may

include e.g., strengthening, task specific training, proximal control, balance and stretching exercises. This situation probably reflects the developing but incomplete scientific frame of reference underpinning exercise and physical therapy interventions for people with ataxia (Ilg et al. 2012). The broad range of interventions and the wide variation in dose, provided in all studies included in this review, may also reflect the lack of consensus about the best approach to take in this field of research.

Five out of the 11 studies where data could be extracted and one third (n= 3) of the studies where data could not be extracted used a form of virtual reality/video game training. Technology-driven interventions appear popular given that seven of these studies were published after 2012. Virtual training will be discussed further in Chapter Seven to demonstrate the scope of its use in neuro-rehabilitation and justify its use in subsequent phases of this study.

Rehabilitation for children with ataxia in line with generic neuro-rehabilitation principles is also targeted at motor learning and adaptation, but it is not clearly understood if individuals with cerebellar dysfunction show similar learning dependent neuroplasticity to that demonstrated in other areas of the injured brain. A greater understanding of cerebellar neuroplasticity would provide a firmer foundation for developing exercise and physical therapy interventions to improve outcomes (Johnston 2009). E.g., future studies of exercise and physical therapy for children with ataxia would benefit from including brain imaging to help determine how the brain responds to training protocols of different intensities and may indicate whether neuroplastic changes occur in the cerebellum and/or other parts of the brain (Ilg et al. 2014). Rasooli et al. (2017) conducted one of the few studies found to date that combined brain imaging with paediatric physiotherapy and demonstrated an increase in fractional anisotropy of the cerebellum indicating a positive effect (a feature for quantifying structural changes in the cerebellum evaluated from diffusion tensor imaging) in four children with cerebral palsy who had balance problems who underwent treadmill training.

Further work in this area may help to tailor interventions by offering an understanding of the relationship between beneficial outcomes and the frequency, intensity and duration of the intervention. It would also be important to determine e.g., whether positive responses to interventions are related to improvements in ataxia-specific impairments or other training effects such as improved strength or cardiovascular endurance, and/or reduced pain, fatigue or falls which were rarely measured in the studies included in this review.

Over forty different outcome measures were used in the twenty studies included in this review. The majority of measures focussed on balance and walking, and gross motor function. Ataxia severity, dexterity, and coordination were rarely reported. Some measures were reported as valid and reliable for children with ataxia. Only one study reported participation level outcomes (PODCI and PSPCSAYC), and two studies used the PEDI which straddles activity and participation domains. A core set of standardised, valid and reliable measures operating at the impairment, activity and participation levels should be developed for future studies and to facilitate meta-analyses, and should be incorporated into a reference group of agreed measures. The SARA and BARS are valid and reliable measures for determining the severity of ataxia in children with posterior fossa tumours (Hartley et al. 2015), and paediatric normative values for the SARA are available (Lawerman et al. 2017a). However, the responsiveness of these scales is not established in paediatrics. A wide range of valid and reliable participation measures for paediatric healthcare focused on well-being and mental health have been developed (e.g. Deighton et al. 2014) and should also be incorporated into core sets. Data that has established norms for the progression of FRA is also now available (e.g. Friedman et al. 2010) and can be used for comparison to measure the effectiveness of interventions over the long-term, and for calculating sample sizes.

3.4.1 Limitations

Despite a comprehensive literature search being undertaken to identify studies concerning physical therapy and exercise interventions for children with ataxia it is possible that some papers may have been missed. However, the search identified all the studies involving children reported in other reviews, and additional studies that had not been previously reviewed. Full text screening was undertaken for a significant number of papers, as reported in Figure 3.1, as it was not clear, through title and abstract screening, whether children were participants. Clearer use of indexing and key words would therefore be of value to more easily identify studies for future systematic reviews as research in this field grows. As discussed in the results, it was not possible to extract data from studies with mixed populations as the results from participants with ataxia were not reported separately. This meant that the overall reporting of results refers to a small number of children, however, this does reflect the limited number of studies with homogeneous patient groups, and the small number of studies undertaken to date with children with ataxia. It is also acknowledged that the literature search was not registered with PROSPERO (International Prospective Register of Systematic Reviews), and this may have limited the awareness of this piece of work.

3.4.2 Conclusions and implications for Phases 1-4

This chapter provides an up to date review of the literature regarding physical therapy and exercise interventions for children with ataxia. The results highlight the lack of rigorous research undertaken to date for this population, despite physical therapy interventions being a mainstay of treatment for this group of children. Key limitations of the reviewed studies included small participant numbers, absence of reporting of patient and public involvement in the planning of the studies, low methodological quality, heterogeneity in the nature of the populations and outcome measures used, and lack of long-term follow up. Positive short-term trends were reported in the reviewed studies, suggesting that the tested interventions have potential therapeutic value. However, it is not possible to make formal

recommendations for clinical practice based on the findings of this systematic review in view of the grading of evidence (studies graded as level 3 and 4 OCEBM).

The results of this systematic review indicate that high quality, child-focussed, studies are urgently needed and provides evidence for the need for the study which is presented later in this thesis, the ASsessment and Physiotherapy managEment of Children with ataxia following surgical resection of posterior fossa Tumour (ASPECT) study. Results from RCTs with adults are not directly applicable to children, which add impetus to the need to carry out further research with children. Ataxia significantly impacts children's access to education, and participation in everyday activities and future life opportunities, it is therefore important to consider what would constitute optimal physical therapy led interventions for this population.

Intervention studies should draw on theoretical principles, experimental neuroscience and motor learning studies, and other practical observations of what is likely to work in children with cerebellar damage. Feasibility studies should be undertaken before engaging in fully scaled RCTs. Well-designed SCEDs with small groups of children may also help to test possible interventions and delivery configurations, and would produce outcome measure data that could inform larger trials. Further attention to the development and testing of existing outcome measures for children, as well as consensus agreements about which measures should be used, would also strengthen trial design and facilitate comparisons across studies. Quality of life and participation measures should be recognised as a fundamental requirement. Where possible imaging results should be reported. Parents and children should be involved in study design, and interventions, including type and delivery dose, as well as fidelity to protocols, should be clearly reported to allow efficacy and effectiveness to be determined. Multi-centre and international collaboration may be necessary to recruit sufficiently large samples for RCTs.

This programme of work addresses elements of the knowledge gap that have been highlighted. The literature review provided support for the completion of a feasibility RCT in a homogenous patient group. It also provided background knowledge to inform treatment choice and intensity for Phase 4 of this study, with the use of virtual training noted as an emerging trend. Although there was wide variation in treatment dosage for studies (where data could be extracted), the median length of intervention (12 weeks), frequency (3 times per week) and session length (37.5 minutes) provided initial information for Phase 4 of this study. (For all 20 studies, median length of intervention was 7 weeks, frequency 3 times per week, session length 45 minutes as previously stated). The literature review also demonstrated the need to consider outcome measure selection carefully in RCTs, with a need to include participation and quality of life measures.

The next chapter will demonstrate how different phases of the ASPECT study will build to address the knowledge gap regarding physiotherapy input for children with ataxia following surgical resection of posterior fossa tumour.

Chapter 4 – Overview of the four phases of the study

4.1 Introduction

This chapter will begin by presenting the involvement of families in the development of the research questions. This patient and public involvement (PPI) in conjunction with the identification of the knowledge gap as identified in Chapter 3 (and direct clinical need as raised in Chapter 1) was instrumental in developing the overarching research question and aims of the PhD programme which are presented below. The aims, objectives and design of each phase of the study are then presented to demonstrate how each phase links together and contributes to the overarching research question.

4.2 Patient and Public Involvement in development of the research questions

A PPI group of three families was established in conjunction with the Comparison of Ataxia Rating Scales (CARS) study. (Family 1, mother and father of a girl who was diagnosed with a brain tumour aged 9; Family 2, mother and father of a boy diagnosed at the age of 11; Family 3, mother and father of a teenage girl who was diagnosed at the age of 14). All of the children had previously undergone neurosurgical management of a posterior fossa tumour (PFT) and also required physiotherapy input post-operatively. Views were predominantly received from parent(s) of the children although feedback was also received directly from two of the older children. Although the focus of the CARS study was on assessment of ataxia and the families understood the need for accurate assessment, the priorities they raised centred on what type/intensity of physiotherapy was best for their child. One family commented "*the question of what type and how many times [to do physiotherapy] go to the heart of the best way to rehabilitate brain tumour survivors*". Although families recognised the importance of understanding how long children can improve for/how long to continue with physiotherapy for, they raised their personal experience of continuing to seek ongoing physiotherapy even after recovery had slowed, explaining "*we will just carry on doing everything we can to help her improve for as long as*

we can". Therefore, the families were asked to expand on these particular research priorities in the planning stage of the ASPECT study. From this discussion, following collaboration with the CARS research team, a list of five research questions were determined that were then given to the original three families and two further families (Family 4, a guardian and boy who was diagnosed age 14; Family 5, a mother and father of a teenager who was diagnosed aged 6) who assisted in the planning of the ASPECT study.

Table 4.1 Five questions PPI group asked to rank

Question
1. Does carrying out **more** physiotherapy/exercise improve coordination?
2. What **type** of physiotherapy is the best for co-ordination problems?
3. Can **adjuncts** to treatment help e.g. lycra garments or taping?
4. How **many times** do I have to do my physiotherapy to help?
5. How **long** after surgery can improvements in coordination be seen?

They were asked to rank the questions (1-5, where 1 was the most important and 5 the least important). The two questions that the families ranked as most important were:

1) Does carrying out more physiotherapy/exercise improve co-ordination?; and
2) what type of physiotherapy is best for co-ordination problems?

Thus, the priorities the families deemed most important, helped to inform the planning of the study in the early stages. The views and perspectives of the PPI group were considered alongside the strengths and limitations of the literature based on the findings of the systematic literature review. These elements combined helped to develop the research questions. The ultimate priority, in view of family feedback and the lack of literature in this area, was to determine the feasibility of conducting a RCT examining the effectiveness of a selected physiotherapy intervention in children with PFT. In order to conduct a RCT the research team also acknowledged the need to confirm that the proposed outcome

measures (i.e. ataxia scales) were appropriate to use in this population group. As a result, three core research questions were developed.

4.3 Overarching research questions

1) What are the most appropriate scales to assess ataxia in children with posterior fossa tumours?
2) What is the range and current scope of current physiotherapy practice and what are the specific challenges physiotherapists face in working with children with PFT?
3) Is it feasible to conduct a RCT studying the effectiveness of a physiotherapy intervention (virtual training) in this population group?

Virtual training was selected as the intervention initially guided by the literature review which highlighted that 8 out of the 20 studies identified used a type of virtual reality technology as their intervention (this was the most common intervention choice). This intervention appears to utilise the principles of motor learning which are of value in this population group (Cheung et al 2014). This was then discussed with the PPI group who agreed there was potential for its use. The xbox Kinect was selected in particular due to no requirements for a controller or balance board which could be challenging in children with ataxia.

4.4 Overarching aims

1) To identify valid, reliable and responsive outcome measures to assess severity of ataxia in children with PFT in the acute and long-term population.
2) To understand the range and scope of contemporary physiotherapy interventions, outcome measurement and the specific difficulties physiotherapists face when working with children with PFT.
3) To determine the critical feasibility components for conducting a RCT about the effectiveness of a physiotherapy intervention for this population with respect to

recruitment, sampling, sample size, intervention design and delivery and acceptability.

4.5 Overview of the design of the four-phased study

In order to fulfil the aim of the study, four phases were developed with Phases 1-3 building to inform the final phase (the feasibility RCT) with the plan for each phase to be analysed separately prior to the results being synthesised to generate the overall results of the study. Figure 4.1 reiterates the phases of the study (as previously presented in Chapter 1), and illustrates how the systematic literature review informed all phases of the study. Phase 1 and 2 were carried out concurrently and used to inform the planning of Phases 3 and 4. An overview of these phases is presented in terms of aim, objectives and design.

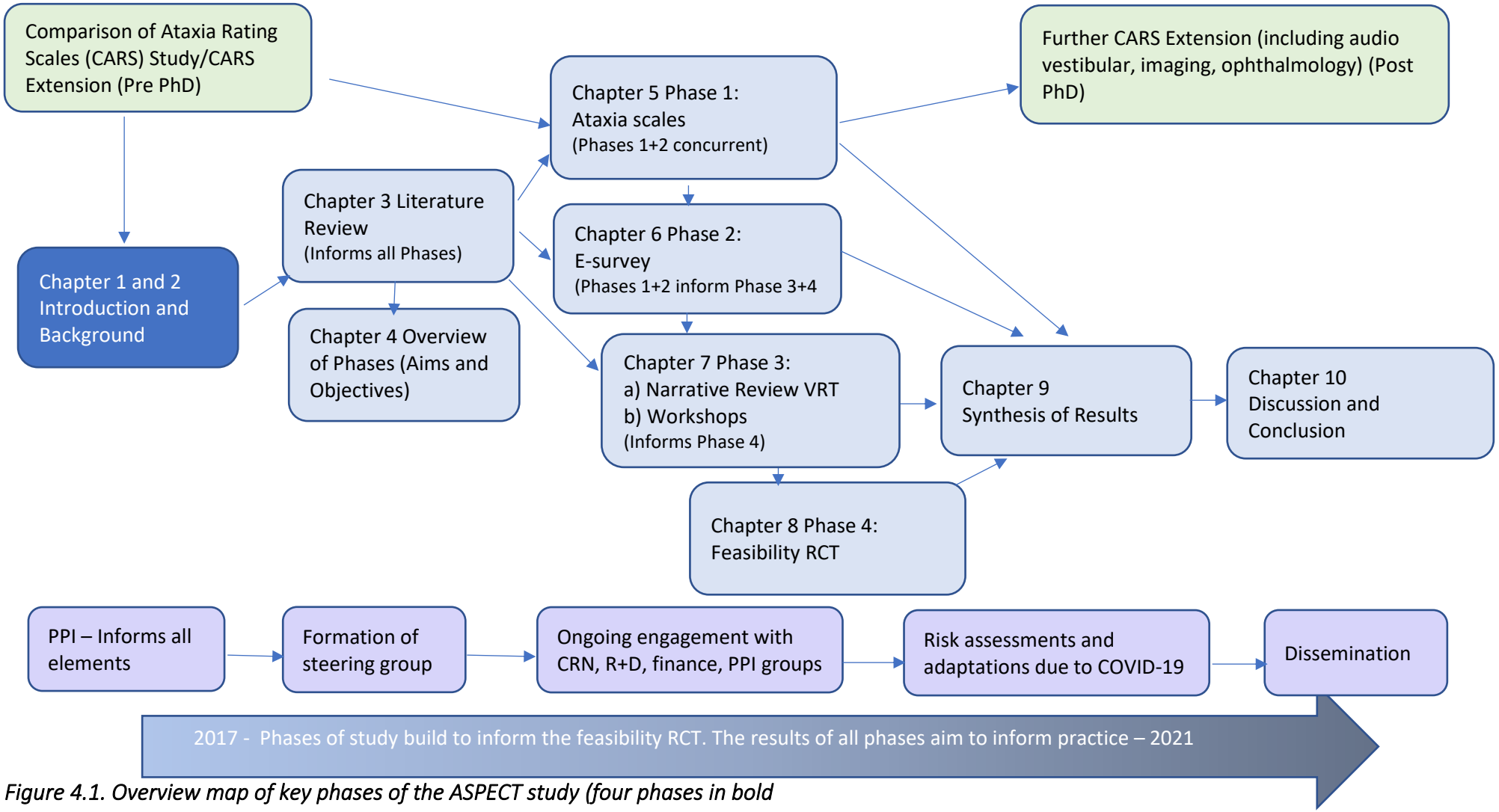


Figure 4.1. Overview map of key phases of the ASPECT study (four phases in bold

4.5 Phase 1 – Establishment of psychometric properties of the SARA and BARS in children with posterior fossa tumours

4.5.1 Aim

The aim of Phase 1 was to inform the use of ataxia scales as an outcome measure for the feasibility RCT (Phase 4).

4.5.2 Objectives

The objectives of Phase 1 were to:

1) Examine the responsiveness of the SARA and BARS rating scales;
2) report floor/ceiling effects, minimally clinically important difference and threshold values of the SARA/BARS for classifying severity of ataxia; and
3) describe the natural history of ataxia in this population group.

4.5.3 Research design and links to other phases

This phase involved the analysis of previously collected data (from the extension to the CARS study) in order to be able to report the psychometric properties of the SARA and BARS scales. Responsiveness (Objective 1) was the particular focus of this phase as this helped to inform the choice of outcome measures for Phase 4 (reliability and construct validity were previously reported in the original CARS study). Objective 2 enabled threshold values of mild, moderate and severe ataxia to be reported which has not previously been described. Objective 3 was achieved by examining change in ataxia over longitudinal assessment time points and informed the inclusion criteria of Phase 4 (regarding time post-surgery).

4.6 Phase 2 – E-survey of current international physiotherapy practice for children with ataxia following surgical resection of posterior fossa tumour

4.6.1 Aim

The aim of Phase 2 was to determine current international practice regarding physiotherapy input for children with ataxia following surgical resection of posterior fossa tumour, and to understand the specific difficulties physiotherapists face when working with this population group.

4.6.2 Objectives

The objectives of Phase 2 were to:

1) Gain an increased understanding of current international physiotherapy practice in relation to treatment methods so as to:
   - identify the most frequent physiotherapy treatment methods used; and
   - identify the most frequent adjuncts to treatment used;
2) understand the challenges to rehabilitation in children with PFT;
3) explore physiotherapists' views of benefits and challenges of using virtual training in this population group;
4) generate an understanding of the range of the dosage of physiotherapy treatment (duration, frequency, intensity), and timing of treatment; and
5) inform the subsequent phases of the larger study, in particular the rationale underpinning the feasibility RCT in relation to intensity and timing of treatment.

4.6.3 Research design and links to other phases

In Phase 2, an e-survey was conducted utilising Survey Monkey™ gathering physiotherapists' views across different countries on current reported physiotherapy input for children with ataxia following surgery for posterior fossa tumours. The survey identified the range of treatment used and helped to develop the understanding of the parameters of use of treatment typically used. This information confirmed the suitability of the type and

intensity of the intervention for the feasibility trial in Phase 4. It was also widened to gain an understanding of the challenges to rehabilitation for this population group. Based on synthesis of the literature review, Phase 2 and PPI, virtual training technologies became the focus of Phase 3, specifically the use of the Xbox Kinect.

4.7 Phase 3 – Workshops – Exploration of innovative technologies for use as virtual training intervention

4.7.1 Aim

The aim of Phase 3 was to inform the choice of video games to be used in the feasibility RCT (Phase 4).

4.7.2 Objectives

The objectives of Phase 3 were to:

1) Identify appropriate virtual training games with a particular focus on Xbox Kinect games; and
2) explore additional software that can link with the Kinect that would be child friendly, appropriate to use in this population and enable progress/compliance to be recorded.

4.7.3 Research design and links to other phases

Phase 3 consisted of two workshops with patients, families and clinical experts to assist with game choice for the feasibility trial (Phase 4) and also to ensure the type of physiotherapy treatment planned for the trial was practical to be carried out both in the hospital and home setting. This enabled ongoing involvement of children and their families in this phase of the study whilst also considering their views in confirming the protocol for Phase 4.

4.8 Phase 4 – Feasibility RCT examining the effectiveness of physiotherapy intervention (virtual training) on ataxia in children following surgical resection of posterior fossa tumour and embedded qualitative study

4.8.1 Aims

The aims of Phase 4 were to:

1) Determine the feasibility of conducting a RCT examining the effectiveness of virtual training on ataxia in children following surgical resection of posterior fossa tumour; and
2) explore children's/parent's perceptions of feasibility and acceptability of virtual training.

4.8.2 Objectives

The objectives of Phase 4 were to:

1) Examine process measures (e.g. number of children identified and subsequently recruited, willingness to be randomised, number of children who complete all assessments);
2) examine intervention measures of the hospital and home-based sessions (e.g. number who complete all intervention sessions, adherence of home training programme);
3) assess the appropriateness of the outcome measures (include any issues with completion of specific outcome measures, and ease of use in the clinical setting);
4) gain an understanding of the child's and parent's perceptions of virtual training and factors influencing acceptability, practicality and adherence to continuing this intervention at home; and
5) provide data to inform sample size for a future definitive fully powered trial (using measures of recruitment rate, drop out, withdrawal, non-completion and group variability of outcome measures).

4.8.3 Research design

Phase 4 was a feasibility RCT examining the effectiveness of virtual training in children with ataxia following surgical resection of PFT. This was a small study evaluating feasibility, therefore the results focused on aspects such as the number of children that entered the study, how many completed all the virtual training sessions (fidelity) and whether the correct outcome measures were chosen. The use of a mixed methods design with an embedded qualitative component using selected process, intervention and outcome measures aimed to help gain an increased understanding of the feasibility components.

Each phase is now presented in detail in subsequent chapters of the thesis.

Chapter Five – Phase 1 – The psychometric properties of the SARA and BARS scales

5.1 Introduction

5.1.1 Use of outcome measures in children with Posterior Fossa Tumours (PFT)

Outcome measures examining quality of survival are important in the management of children with PFT as they can provide information about pre-operative presentation, determine the impact of interventions (e.g. neurosurgery, radiotherapy), and identify the effectiveness of rehabilitation.

Ataxia is the most common motor deficit occurring in children with PFT as discussed in Chapter 2. There is minimal evidence in the literature to determine how ataxia is measured in the clinical situation, which makes it difficult to objectively establish if ataxia has changed following surgical intervention or rehabilitation. Therefore, there is a particular need for a validated outcome measure to assess the severity of ataxia in this population group.

5.1.2 SARA and BARS in children with PFT

SARA (Schmitz-Hubsch et al. 2006) and the BARS (Schmahmann et al. 2009) are the two most commonly described ataxia scales used both clinically and in research in acute paediatrics. The other well-known scale the ICARS, as noted in Chapter 2 is not typically used in acute clinical practice. The SARA scale (Appendix 1) has eight items (gait, stance, sitting, speech, finger chase, finger nose, rapid alternating hand movements and heel along shin) and a higher score represents more severe ataxia (total score 40). The BARS scale (Appendix 2) has five items (gait, finger to nose, heel along shin, speech and oculomotor), again a higher score reflects more severe ataxia (total score out of 30).

In Chapter 2.6 the literature on the use of the SARA and BARS to date was presented, and it was noted that the SARA has now been validated in specific areas of paediatrics. In healthy children, inter-rater reliability has been determined, and age-related reference values have been developed (Lawerman et al. 2017a). In early onset ataxia, good reliability (inter and intra rater) has also been reported (Brandsma et al. 2017). However, discriminant validity was low, and the SARA could not determine 'ataxia severity' specifically when examined with severity of other ataxia concurrent movement disorders (Brandsma et al. 2017). No validation in the paediatric population has been carried out for the BARS, except for assessment of reliability and construct validity in children with PFT which was conducted for both the BARS and the SARA as part of the original CARS study. However, despite this, the BARS has been adopted to measure cerebellar symptoms in recent international paediatric neuro-oncology trials (PNET 5 Clinical Trials Reference; NCT02066220 and NORDIC Cerebellar mutism study NCT02300766), although the reason for this choice is not stated.

Both scales are based at the level of impairment assessment (according to the World Health Organisation ICF framework 2001), therefore, in the later post-operative rehabilitation stage of the child's management, these ataxia scales may need to be supplemented with outcome measures focused on activity and participation to measure the broader effectiveness of therapy intervention. Both scales offer the potential of a quick and easy to complete assessment focused on the most common movement problem in children with PFT, that can be carried out by different professionals from various disciplines in both the pre-operative and acute post-operative phase. However, the psychometric properties of these scales have not been fully evaluated in the paediatric PFT population. In particular there is a lack of data about responsiveness, floor and ceiling effects and minimally clinically important difference (MCID). Cut off values or thresholds for severity indicators are also unknown. There is also a lack of information about the natural history of ataxia in this population group which would help to understand potential for improvement, and assist in

educating families about prognosis. This knowledge may also assist with the timing and targeting of rehabilitation efforts.

In this chapter the analysis of previously collected but unexamined data from the Comparison of Ataxia Rating Scale (CARS) study is presented. The CARS study was initially established in 2012 to examine the reliability and construct validity of the SARA and BARS in children with PFT (with myself as Chief Investigator). It was subsequently extended in 2014 to facilitate the collection of longitudinal data. The analysis represents data collected between 2012-2019 (closed to recruitment in 2017, but ongoing longitudinal assessments for those already recruited).

5.1.3 Psychometric properties of outcome measures

There are a number of different properties that should be considered when deciding if an outcome measure is of value for use in a particular population group. These elements include clinical utility, validity, reliability, and responsiveness (APCP 2005, Terwee et al. 2007).

Clinical utility (practicality or feasibility for use within a clinical context) is essential (Terwee et al. 2007). The tool should be easy to administer, score and interpret in different settings, cost effective, and consider the time burden for the patient and clinician (APCP 2005, Mokkink et al. 2018a). This is of particular relevance for children with PFT where outcome measures may need to be applied to a wide age range of children with differing communication and cognitive abilities. Equally children may be unwell in the acute stages of medical management, or have issues with fatigue, therefore the ability to complete the required physical components of assessment for the outcome measures in a timely manner is important.

The quality of an outcome measure can be evaluated across three domains: reliability, validity and responsiveness (Scholtes et al. 2011). Each domain contains one or more measurement property. Reliability which relates to the repeatability of the instrument and

refers to the extent the tool will produce the same score when it is repeated, contains three measurement properties: internal consistency, reliability and measurement error. The validity domain contains three measurement properties; content validity (includes face validity), construct validity (encompasses structural validity, hypotheses testing, and cross-cultural validity) and criterion validity (Mokkink et al. 2018a). Criterion validity is assessed by testing the instrument against an already accepted accurate measure, sometimes referred to as gold standard (Sim & Arnell 1993). This can be difficult, particularly for rehabilitation outcome measures, as it is rare that a gold standard already exists; this is the case in children with PFT. Where criterion validity cannot be demonstrated, construct validity may be examined. Definitions for each measurement property as used within this study are presented below.

Table 5.1 Definitions of measurement properties (Mokkink et al. 2018a COSMIN User Manual, p12.)

Term			**Definition**
Domain	Measurement Property	Aspect of a measurement property	
Reliability			The degree to which the measurement instrument is free from measurement error
	Internal consistency		The degree of the inter relatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to true differences between patients
	Measurement error		The systematic and random error of a patient score that is not attributed to true changes in the construct to be measured
Validity			
	Content validity		The degree to which the content of an outcome measure is an adequate reflection of the construct to be measured
		Face validity	The degree to which items of an outcome measure indeed looks as though there are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an outcome measure are consistent with hypotheses based on the assumption that the outcome measure validly measures the construct to be measured
		Structural validity	The degree to which the scores of an outcome measure are an adequate reflection

			of the dimensionality of the construct to be measured
		Hypotheses testing	Idem construct validity
		Cross cultural validity	The degree to which the performance of the items on a translated or culturally adapted outcome measure are an adequate reflection of the performance of the items of the original version of the outcome measure
	Criterion validity		The degree to which the scores of an outcome measure are an adequate reflection of a gold standard
Responsiveness			The ability of an outcome measure to detect change overtime in the construct to be measured
	Responsive-ness		Item responsiveness
Interpretability			Interpretability is the degree to which one can assign qualitative meaning, i.e. clinical or commonly understood connotations, to an outcome measures quantitative scores or change in scores

The responsiveness domain contains only one measurement property. Responsiveness (also referred to as sensitivity to change) is the ability of the tool to detect change over time in the construct to be measured (Mokkink et al. 2010b). In essence it refers to the validity of a change score. Appropriate measures to assess this are the same as for hypotheses testing and criterion validity; however, the focus in this instance is on change score (Mokkink et al. 2018b).

Interpretability is not considered a measurement property (Mokkink et al. 2018a) but an important characteristic of a measurement instrument. The COSMIN risk of bias checklist considers distribution of scores in the study population, percentage of missing items and percentage of missing total scores, floor and ceiling effects, scores and change scores for relevant subgroups and minimal important change (MIC) or minimal important difference (MID) as relevant information to assess interpretability.

It is important to assess psychometric properties in each study population of interest to ensure the measures are sufficiently accurate and responsive to detect a meaningful difference as each population can have its own unique presenting characteristics (Turner

Stokes 2000); in this case the population of interest is children with PFT. Variability in ataxia due to factors such as fatigue, are important to consider as these may affect properties such as reliability and MIC.

5.1.4 COSMIN checklist

Following initial work by Terwee et al. (2007), recommendations have been produced by the COSMIN group (COsensus-based Standards for the selection of health Measurement INstuments) regarding selecting health measurement instruments. A COSMIN manual and checklist to evaluate methodological quality of studies on measurement properties were initially developed by Delphi-study method (Mokkink et al. 2010a). These have been superseded by versions published in 2018 (User Manual COSMIN, Mokkink et al. 2018a, Risk of bias checklist Mokkink et al. 2018b). Although designed to assess quality of studies (particularly focused on patient reported outcome measures (PROMs)), they are also recommended for consideration when reporting studies on outcome measures and additionally provide useful definitions of measurement properties. The 10 items on the updated COSMIN checklist (2018b) are:

1) PROM development;
2) Content validity;
3) Structural validity;
4) Internal consistency;
5) Cross-cultural validity;
6) Reliability;
7) Measurement error;
8) Criterion validity;
9) Hypotheses testing for construct validity; and
10) Responsiveness.

For each checklist topic there is a box which includes a number of items which should then be considered for each topic (Appendix 5), e.g., with respect to responsiveness (construct approach) ‘is it clear what the comparator instrument measures’, and ‘was the statistical method appropriate’ (Mokkink et al. 2018 p35).

COSMIN recommendations have been considered throughout the reporting of psychometric properties of the SARA and BARS presented in this chapter.

5.2 Aim

The aim of this study (Phase 1) was to identify an ataxia scale to measure ataxia at an impairment level to use as an outcome measure for the feasibility RCT (Phase 4).

5.3 Specific objectives

The objectives of this study (Phase 1) were to:

1) Examine the responsiveness of the SARA and BARS rating scales;
2) report floor/ceiling effects, minimal clinically important difference and threshold values of the SARA/BARS for classifying severity of ataxia; and
3) describe the natural history of ataxia in this population group.

5.4 Study design – CARS study

The CARS study and its extension was already underway prior to the commencement of this PhD programme of work (ASPECT study), so the focus for the ASPECT study was data analysis of previously collected but unexamined data. Taking this into account, only a brief summary of methods is presented in this chapter to provide an overview of the elements of the design of the CARS study.

5.4.1 Inclusion/exclusion criteria

Children with a PFT, aged between 4 and 18 years, who were under the care of a tertiary neuro-oncology team were eligible for inclusion in the original CARS study. Children were

excluded if they were medically unstable or had significant learning disabilities which meant they were unable to participate in the assessments.

5.4.2. Recruitment

Children were identified by the neuro-oncology team at the tertiary treatment centre. If the child was newly diagnosed with a PFT and was an inpatient, they and their parent(s) were approached and given relevant study details (parent and age-appropriate participant information sheets). Parents of children who were outpatients under the follow up care of the neuro-oncology team were first sent an invitation letter, along with written information sheets, four weeks prior to their scheduled clinic appointment to allow consideration of the information. Parents were then approached by the CI (myself) to allow them the opportunity to ask questions about the study and then, if they wished to proceed, informed consent was sought. The Chief Investigator (who had Good Clinical Practice (GCP) training and additional informed consent training) gained written consent.

5.4.3 Assessment procedures – CARS Study

The initial CARS study focused on the inter-rater reliability and the construct validity of the SARA and BARS. The children were rated independently by two raters (from a pool of three) who were experienced paediatric neuro-physiotherapists. The raters completed the SARA, BARS and the mobility domain of the Paediatric Evaluation of Disability Index (PEDI-m). The PEDI as discussed in Chapter 2 (Section 2.5) has stand-alone mobility, self-care and social interaction domains. The mobility domain includes items such as transfers, indoor and outdoor mobility and stairs. A higher score represents better mobility. They also recorded a Global Clinical Impression (GCI) of ataxia severity (categorised as no, mild, moderate or severe). The GCI was recorded at the end of the assessment and assessors were asked to specifically consider ataxia severity based on their assessment findings when recording this. The PEDI was chosen as it is the only validated functional measure in paediatric acquired brain injury, and it is also similar in scope to the activities of daily life

(ADL) scales that have been used in the validation of the ataxia scales in the adult population. The order of completion of rating scales was randomised to minimise fatigue and practice effects (randomisation undertaken by a statistician). The time taken to complete each scale was also recorded. The rater protocol is detailed in Appendix 6.

Data analysis and the results of the original CARS study which included 44 participants are presented in Appendix 7 for reference. These illustrate good inter-reliability and construct validity, alongside feasibility in terms of how long the scales took to complete (Hartley et al. 2015).

5.4.4 CARS extension procedures

The CARS study was then subsequently extended via a substantial amendment to the North West Liverpool East Research Ethics Committee (02/09/2013) to include longitudinal assessments for the purpose of examining responsiveness of the scales and also to describe the longitudinal nature of ataxia in children with PFT. The same assessment measures (SARA, BARS, PEDI-m and GCI) from the original study were used. The parents and child (where appropriate) and the physiotherapists were also asked to record their impression of change of ataxia from their last assessment specifically (GCI-Change) from significantly worse to significantly better on a 7-point Likert Scale (Appendix 8). The Global Impression Scale is a recognised way of recording change in health practice (Busner & Targum 2007). This was completed at the end of the assessment.

Participants who had already been recruited and were eligible for ongoing assessments were re-consented using the informed consent process. Children who were under long term outpatient follow up were assessed at a subsequent clinic appointment if they wished to continue to take part in the study (this was typically a year on from their initial assessment).

Participants (aged between 4 and 18 years) recruited for the first time after the amendment were newly diagnosed children who were assessed from the time of diagnosis; these children were inpatients at the time of recruitment. Assessment time points were; post-

operatively (defined as within 1 week of surgery), 3 months post-operatively, 1-year post-operatively, 2 years post-operatively, 3 years post-operatively, and 5 years post-operatively. The methodology chosen was similar to that used in other comparable studies such as those examining the responsiveness of the Berg Balance Scale in the adult population (Mao et al. 2002, Wood-Dauphine et al. 1997).

5.5 Ethical issues

Ethics approval and local research and development approval was obtained for the CARS study and subsequent amendments were gained via the IRAS process (IRAS ID 98449). Participant information sheets were prepared for different ages of children (and cognitive ability), and the child and their parents were given time to consider the study information prior to the consent process (parents consented on the child's behalf, assent forms were also available for children who were able to understand the requirements of the study). The children and their parents did not have to attend the study hospital for any additional visits as part of the CARS study, and the assessments were completed either as an inpatient or when they were attending clinic appointments. The assessment measures reflected those used in routine clinical practice and were quick to complete for the participants.

The study population included children with malignant tumours who have the potential to relapse from their disease and may have a poor prognosis, therefore reporting systems were in place to inform the Research Ethics Committee (REC) of any adverse events such as tumour progression. The neuro-oncology team informed the study team in the event of deterioration or where the child had died to ensure parents were not contacted in these circumstances.

5.6. Research governance

Each participant was given a study ID and on entering the study all data were anonymised. Anonymised data were entered onto a secure database accessible to the CI and statistician only. The CI and statistician were responsible for data analysis. Data storage was in line

with the Data Protection Act 1998 and subsequently aligned to the General Data Protection Regulation (GDPR) 2018 and NHS Code of Confidentiality/Trust Policy. All essential documents will be archived for 10 years after completion of the trial.

5.7 Data analysis

5.7.1 Whole cohort (cut off values, floor/ceiling effects)

The following analysis was carried out for all participants recruited to the CARS study from the date of opening in June 2012 to closing to recruitment (including participants recruited in the extension period) in February 2017.

Initially the data were summarised using descriptive statistics (including age at recruitment, age at diagnosis, tumour location and tumour histology). Process measures were then reported (participants who met inclusion criteria, number who were recruited, number who completed the full assessments).

Cut off values were determined (for no, mild, moderate and severe ataxia) with the use of sensitivity and specificity curves. The cut off values were identified where the sensitivity and specificity curves cross. Floor and ceiling effects were reported (the number of participants who scored the lowest or highest possible scores) for the SARA, BARS and PEDI-m.

Descriptive statistics were also described for the two cohorts of participants: ‘acute participants’ (children who were assessed from within one week post-operatively and followed longitudinally), and ‘stable participants’ (children who were initially assessed two years or more post operatively and reassessed in clinic 12 months later).

5.7.2 Responsiveness

Responsiveness (the ability of the SARA and BARS to detect a change in ataxia) was also analysed. Different methods are available to analyse these data, and in this case, as there was no gold standard to measure against, anchor based and hypothesis testing methods

are presented. These were informed by the checklists for responsiveness in the COSMIN criteria as previously detailed (Appendix 5).

5.7.2.1 Analysis of change compared with (global) clinical impression of change

The change scores of the scales were mapped against the (global) clinical impression of change (GCI-Change) (i.e. using the GCI-change as an anchor measure). The SARA and BARS change scores (between assessments) were initially presented in table format. Box plots were then drawn and analysis completed to ascertain any significant difference in the change score between the groups of participants rated same, minimally better and much better. Data were then used to inform an initial impression of MCID based on statistical analysis.

5.7.2.2 Correlation of SARA change with BARS change

The correlation of the SARA change score with the BARS change score was graphically scatter plotted and correlation coefficients were calculated using Spearman's rank correlation coefficient (rho). Non-parametric tests were conducted as the data was not normally distributed.

5.7.2.3 Construct Approach (hypothesis testing) between subgroups and pre- and post-operative

A construct approach of hypothesis testing was then completed using nonparametric testing for two scenarios. Firstly, between subgroups ('acute' and 'stable' participants) and secondly to compare pre- and post-operative assessment scores. The null and experimental hypotheses are stated below.

Between subgroups ('acute' and 'stable participants');

Null hypothesis: There will be no difference in SARA and BARS scores between assessments at 0 and 3 months, and 3 and 12 months.

Experimental hypothesis: There will be a difference in SARA and BARS scores between assessments at 0 and 3 months, and 3 and 12 months.

Conversely no change was expected for assessments completed after 12 months.

To compare pre- and post-operative assessment scores;

Null hypothesis: There will be no difference between pre-operative and post-operative SARA scores

Experimental hypothesis: There will be a difference between pre and post-operative SARA scores

5.7.2.4 Patterns of change

In order to explore how scale data changed over time and the natural history of ataxia from the time of surgical intervention, data was initially graphically plotted (with SPSS) over a three-year period. The main focus of this was the acute participants, providing information on the natural history of ataxia from the time of surgery.

5.7.3 Longitudinal nature of ataxia

Further to patterns of change for acute participants being presented graphically to illustrate scale scores, additional graphical illustration of longitudinal change in ataxia considering different tumour type (medulloblastoma compared with low grade glioma) and tumour location (midline compared with unilateral) was presented. This provided information that was of clinical interest and also an illustration of the ability of the SARA and BARS to identify different population groups. Due to the need for adjuvant oncology treatment, the prevalence for midline location and increased risk of cerebellar mutism, it was hypothesised that children with medulloblastoma would present with more severe ataxia.

5.8 Results

5.8.1 Whole cohort analysis

5.8.1.1 Process measures

Seventy-eight children were recruited to the CARS study between June 2012 and February 2017. Figure 5.1 illustrates how many children were identified and screened for the CARS study and how many children were subsequently recruited.

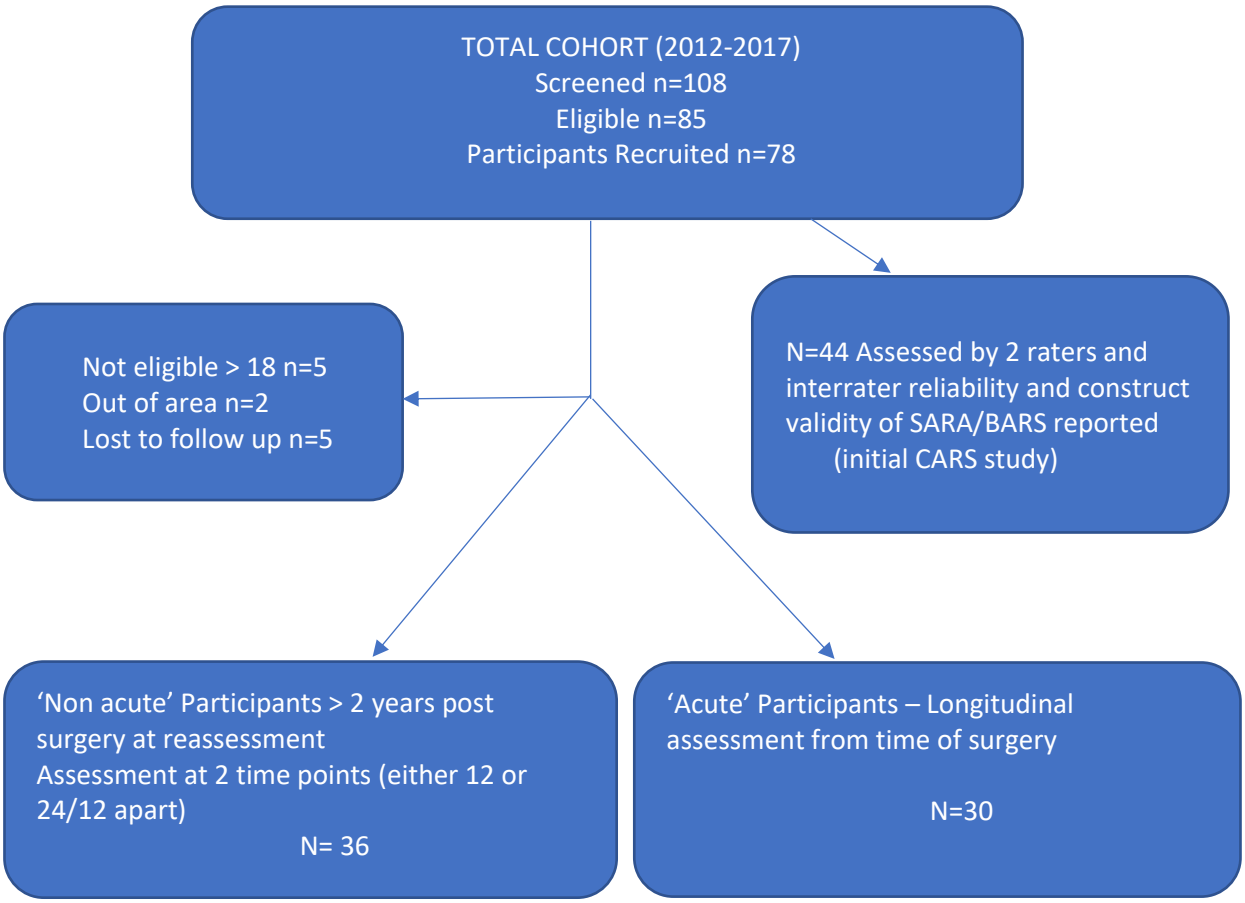


Figure 5.1 Participant identification and recruitment

Eighty-five children (of 108 who were screened) were eligible for the original CARS study, of these 78 were recruited indicating a high recruitment rate of 92%. Sixty-six children were included in the CARS extension study (12 children not eligible either due to being over the age of 18 years, lost to follow up or follow up occurring out of area). Thirty-six children were considered to be in the 'stable' cohort of participants and had assessment at two time points.

Thirty children were ‘acute participants’ and completed assessments longitudinally from the time of surgery.

5.8.1.2 Participant Characteristics

Participant characteristics are illustrated in Table 5.2. Participants’ age ranged from 5 to 18 years. Forty nine percent of participants were diagnosed with a low-grade glioma and 36% of participants were diagnosed with a medulloblastoma. The data were not normally distributed with the majority of children observed to have mild ataxia (i.e. skew in the normal distribution curve to the left), therefore non-parametric methods of analysis were used. At initial baseline assessment SARA score ranged from 0 to 35.5, with the median being 6. BARS scores ranged from 0 to 25 with the median being 4.

Table 5.2 Participant characteristics (n=78)

Characteristic	
Gender	Male 42 Female 36
Age at time of recruitment (years)	Range 5 -18 (median 11)
Years post diagnosis	Range 0-13 (median 1)
Histology	Low grade glioma n= 38 Medulloblastoma n=28 Ependymoma n=9 Other (e.g. schwannoma) n=3
Location	Midline n=48 Unilateral n=27 (missing n=3)
Baseline Assessments SARA BARS PEDI (mobility scaled score)	 Median 6 (IQR 10) Range 0-35.5 Median 4 (IQR 8) Range 0-25 Median 77.3 (IQR 41.1) Range 15.2-100 (No missing items on any assessments completed)

5.8.1.3 Cut off values for severity of ataxia

Cut off values for SARA and BARS to distinguish between no, mild, moderate and severe ataxia are presented in Table 5.3 and Table 5.4. Cut off figures were chosen to optimise

both sensitivity and specificity. Therefore, for the SARA scale the cut off value for distinguishing no ataxia from mild ataxia was 1.75, and 1.5 for the BARS. The threshold for determining mild from moderate ataxia was 7.75 on the SARA and 4.5 on the BARS. The threshold for determining moderate ataxia from severe ataxia was 14.25 on the SARA and 9.5 on the BARS.

In clinical practice only 0.5 interval scores are available on the SARA therefore this would be interpreted clinically for the SARA as a score of 2 as the threshold for distinguishing no ataxia from mild ataxia, a score of 8 to distinguish mild ataxia from moderate ataxia and a score of 14 to distinguish moderate ataxia from severe ataxia.

Table 5.3 Optimum cut-off values SARA (n=78, baseline assessment)

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	Kappa
No – Mild	0.98 (0.94, 1.00)	**1.75***	95.5%	84.6%	96.9%	78.6%	0.78 (0.59, 0.96)
Mild – Moderate	0.95 (0.90, 1.00)	**7.75****	90%	89.8%	84.4%	93.6%	0.79 (0.65, 0.93)
Moderate – Severe	0.98 (0.94, 1.00)	**14.25*****	100%	92.6%	68.8%	100.0%	0.78 (0.59, 0.96)

Only 0.5 intervals available on scale therefore adjusted threshold score for detection of ataxia as follows, rounded to nearest 0.5 integer value;
*2=mild ataxia
**8=moderate ataxia
***14=severe ataxia

Table 5.4 Optimum cut-off values BARS (n=78, baseline assessment)

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	Kappa
No – Mild	0.95 (0.90, 1.00)	**1.5**	93.8%	84.6%	96.8%	73.3%	0.74 (0.54, 0.94)
Mild – Moderate	0.97 (0.94, 1.00)	**4.5**	96.6%	81.6%	75.7%	97.6%	0.74 (0.59, 0.89)
Moderate – Severe	0.98 (0.95, 1.00)	**9.5**	100%	100%	50.0%	100%	0.60 (0.38, 0.81)

5.8.1.4 Floor/ceiling effects of the SARA and BARS and PEDI-m

The number of children who demonstrated the worst possible (floor) and best possible (ceiling) scores on all scales are presented in table 5.5. Fourteen children scored the best possible score on the PEDI-m (17.9%).

Table 5.5 Floor/ceiling effects (n=78, baseline assessment)

Scale	Number who scored worst possible score	Number who scored best possible score
SARA	0	1
BARS	0	4
PEDI-m	0	14

5.8.1.5 Participant characteristics 'acute' cohort

Thirty children were assessed longitudinally from the point of initial surgery as part of the CARS extension. Participant characteristics are presented in Table 5.6. The age range of this cohort was 5 years to 15 years of age. Thirteen children (43%) were diagnosed with a low grade glioma and 12 children (40%) were diagnosed with a medulloblastoma.

Table 5.6 Longitudinal 'Acute' Cohort CARS extension n=30

Characteristic	
Gender	Male 19 Female 11
Age at time of recruitment (years)	Range 5-15 (median 9)
Years post diagnosis	N/A Assessment from immediate post op period (within 1/52)
Histology	Low grade glioma n= 14 Medulloblastoma n=11 Ependymoma n=3 Other (e.g. schwannoma) n=2
Location	Midline n=22 Unilateral n= 8 (missing n=0)

5.8.1.6 Participant characteristics 'stable' cohort

Thirty-six participants who were two years or more post-surgery were assessed at two time points (at clinic visits either 12 months or 24 months apart). These children were deemed

to be ‘stable’ and a significant change was not expected between assessments. Participant characteristics are presented in Table 5.7. The age range of this cohort was five years to 17 years. Seventeen children (47%) were diagnosed with a low-grade glioma and 12 children (33%) were diagnosed with a medulloblastoma. At initial assessment SARA score ranged from 0.5 to 22, with the median being 4. BARS scored ranged from 0 to 20 with the median being 4.

Table 5.7 ‘Stable’ (non-acute) cohort CARS extension n=36

Characteristic	
Gender	Male 18 Female 18
Age at time of reassessment (years)	Range 5-17 (median 11)
Years post diagnosis at reassessment	Range 2-13 (median 5)
Histology	Low grade glioma n= 17 Medulloblastoma n= 12 Ependymoma n= 6 Other (e.g. schwannoma) n= 1
Location	Midline n=22 Unilateral n=11 (missing n=3)
Baseline Assessments SARA BARS PEDI (mobility scaled score)	 Median 4.5, (Range 0.5-22, IQR 9.25) Median 4.0, (Range 0-20, IQR 6.5) Median 85.2, (Range 42.4-100, IQR 29.05)
Reassessment Score SARA BARS PEDI (mobility scaled score)	 Median 5.5, (Range 0 – 17.5, IQR 8) Median 4.0, (Range 0-16, IQR 6.5) Median 82.5, (Range 40.3-100, IQR 23.75)

5.8.2 Responsiveness

5.8.2.1 Analysis of scales compared with clinical impression of change

Analysis was completed to compare change in score of outcome measure (SARA, BARS and PEDI-m) against (global) clinician impression of change (GCI-Change). The clinician impression of change was recorded on a 7-point Likert scale from very much worse to very much better. This was completed in the ‘stable’ cohort where participants were expected to show minimal change. To provide further data, assessments completed at year 2 and year

3 from the acute cohort were added to this analysis (i.e. all of the cohort were two years or more post-surgery). (These data are detailed in Appendix 9 illustrating a similar spread of results across both cohorts and thus it was appropriate to combine the data). This resulted in 59 participants having assessments at two time points to analyse.

(A similar analysis for acute participants assessed between baseline and 3 months, and 3 months and 1-year is presented in Appendix 9 for further information).

Analysis of change in SARA scores over time

The change in SARA scores from assessment 1 to assessment 2 are initially presented in table format (Table 5.8).

Table 5.8 Change in SARA scores between assessments compared with GCI-change (n=59)

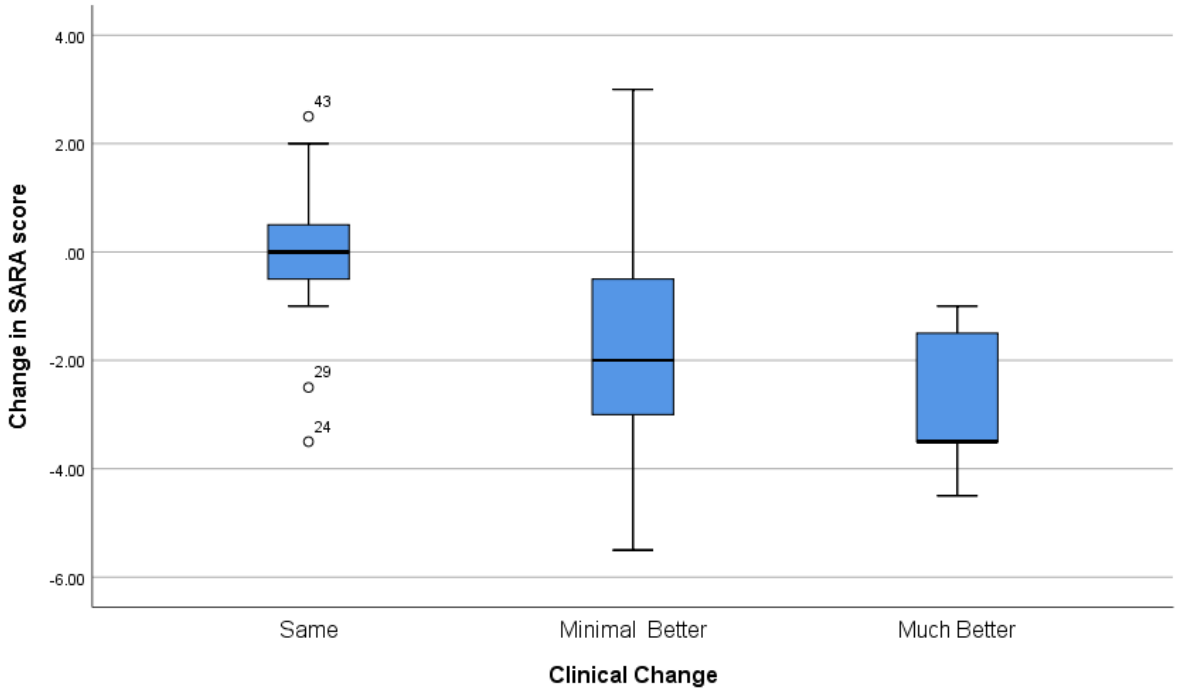
Change	***N***	***Median (IQR)***	***SARA change***
Minimally Worse	1		-4
Same	31	0.0 (1)	
Minimally Better	15	-2.0 (3)	
Much better	5	-3.5 (2.75)	
Missing	7		

Table 5.8 illustrates that 31 out of the 59 participants were rated by the clinicians to be the same at both time points. For the 31 children who were rated the same by clinicians, 27 (87%) of the SARA change scores between assessment one and assessment two were between -1 and +1. The median change for children considered to be minimally better by clinicians was -2. For the 15 children who were reported to be minimally better by the clinicians 10 (67%) of the SARA change scores were between -1 and -3.5. The median change for children considered to be much better by clinicians was -3.5. There is one outlier where a child was reported by the clinician to be worse when their SARA score actually dropped (which would be indicative of an improvement in ataxia severity).

The data suggest that if the SARA change was in the range of -1,+1 then this implied no clinical change. There is overlap between the better categories and no clear boundary

existed. A change of +/-2 indicates a clinical change although there is only one child who was reported as worse and therefore caution should be applied in interpreting the ability of the SARA to detect if the child has deteriorated.

The change in SARA score against GCI-Change is also presented graphically in the box plots in Figure 5.2, with the single outlier excluded.



Same n=31, Minimal better n=15, Much better n=7

Figure 5.2 Change in SARA score against global clinical impression of change

The box plots for the SARA illustrate a trend that would be expected clinically, with a reduction in SARA score for participants rated as minimally better, and a lower score again for participants rated as much better.

Further analysis was also completed to determine the difference between the SARA change score for the three groups (same, better and much better, (median change 0, -2, and -3.5 respectively)) as rated by the clinicians. The Kruskal Wallis test demonstrated there was a significant difference between the groups (p=0.001). Therefore, post-hoc paired tests (Mann-Whitney U test) were then undertaken between the groups. There was a significant

difference in the SARA change score between the group of participants rated as same versus minimally better (p=0.01), and the group rated same versus much better (p=<0.001). There was no significant difference in SARA change score for participants who were rated as minimally better versus those rated as much better (p=0.23).

Analysis of change in BARS scores over time

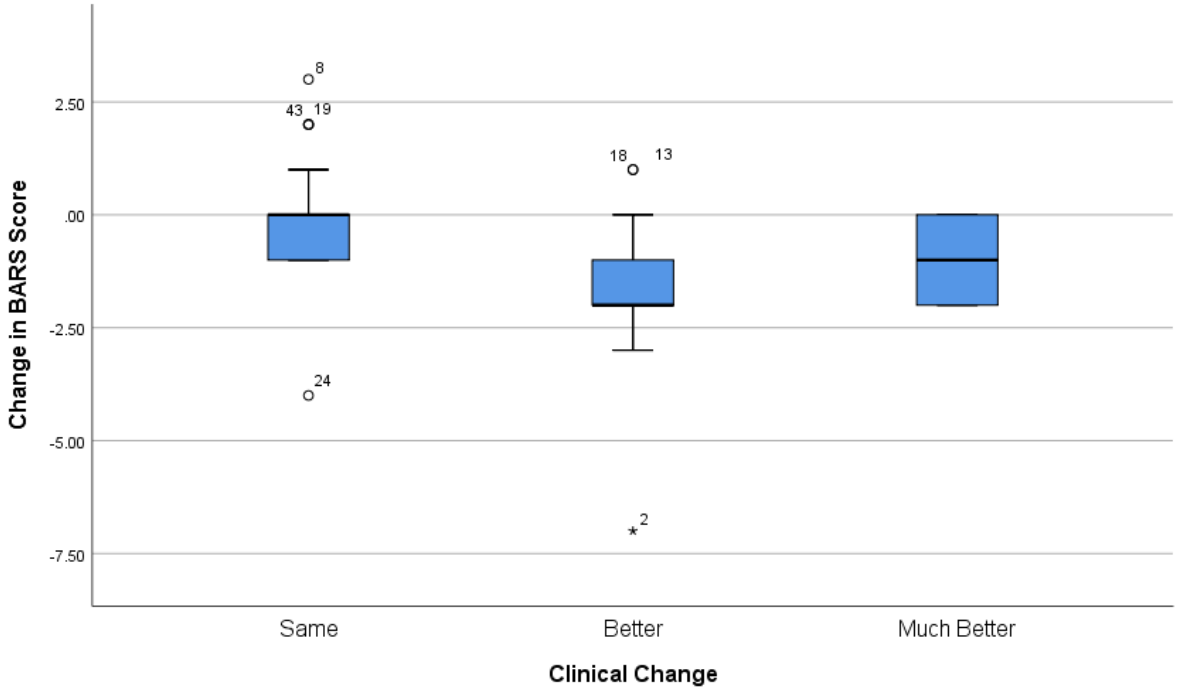
The change in BARS scores from assessment 1 to assessment 2 are initially presented in table format (Table 5.9).

Table 5.9 Change in BARS scores between assessments 1 and 2, compared with GCI-change (n=59)

Change	***N***	***Median (IQR)***	***BARS change***
Minimally Worse	1		2
Same	31	0.0 (1)	
Minimally Better	15	-2.0 (1)	
Much better	5	-1.0 (2)	
Missing	7		

Table 5.9 illustrates 31 out of the 59 participants were rated by the clinicians to be the same at both time points. For the 31 children who were rated the same by clinicians, 25 (81%) of the BARS change scores between assessment one and assessment were between -1 and +1. The median change for children considered to be minimally better by clinicians was -2. For the 15 children who were reported to be minimally better by the clinicians 11 (71%) of the BARS change scores were between -1 and -3. The median change for children considered to be much better by clinicians was -1. The data suggest that a change of +/-2 or larger on the BARS score is required for the clinician to see change in this population group (based on statistical significance). Again, caution is required with interpreting the ability of the BARS to detect deterioration as only one child was reported to be worse on assessment.

The change in BARS score against clinician impression of change is presented in the box plots (Figure 5.3, excluding the single child rated as worse).



Same n=31, Minimal better n=15, Much better n=7

Figure 5.3 Change in BARs score against global clinical impression of change

The trend in the BARS score is not consistent with what would be clinically expected i.e. sequential lower score for participants considered to be minimally better and then much better. However, it should be noted there were only 5 participants who were rated as much better for both the SARA and BARS.

Further analysis was also completed to determine the difference between the BARS change score for the three groups (same, better, and much better, (median change 0, -2, and -1 respectively)) as rated by the clinicians. The Kruskal Wallis test demonstrated there was a significant difference between the groups (p=0.02). Therefore, post-hoc paired tests (Mann-Whitney U test) were then undertaken between the groups. There was a significant difference in the BARS change score between the group of participants rated as same versus minimally better (p=0.001). However, there was no significant difference in BARS change score for participants who were rated as the same versus much better (p=<0.12) which would be unexpected. There was also no significant difference in BARS change score for participants who were rated minimally better versus those rated as much better (p=0.35).

Comparing the two figures suggests that SARA might have more potential to identify subtle clinician perceived change than the BARS. Although caution is noted in interpreting these results due to unequal numbers in each group.

Analysis of change in PEDI-m scores over time

The change in PEDI-m scores from assessment 1 to assessment 2 are initially presented in table format (Table 5.10).

Table 5.10 Change in PEDI-m scores between assessments compared with GCI-change (n=59)

Change	***N***	***Median (IQR)***	***PEDI-m change***
Minimally Worse	1		7.3
Same	31	0.0 (4)	
Minimally Better	15	0.0 (7.7)	
Much better	5	14.4 (27.3)	
Missing	7		

Table 5.10 illustrates 31 out of the 59 participants were rated by the clinicians to be the same at both time points. For the 31 children who were rated the same by clinicians, 21 (68%) of the PEDI-m change scores between assessment 1 and assessment 2 were 0. The median change for children considered to be minimally better by clinicians was 0. The median change for children considered to be much better by clinicians was 14.4.

The change in PEDI-m score against clinician impression of change is also presented in the box plots (Figure 5.4, excluding the single child rated as clinically worse).

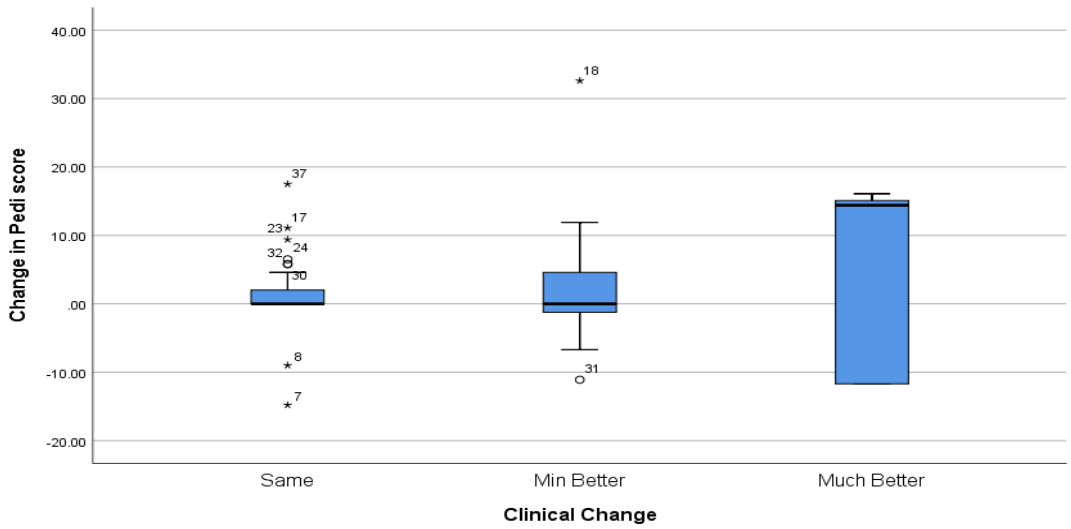


Figure 5.4 Change in PEDI-m score against clinical change

Further analysis was also completed to determine the difference between the PEDI-m change score for the three groups (same, better, and much better, (median change 0, 0, and 14 respectively)) as rated by the clinicians. The Kruskal Wallis test demonstrated there was no significant difference between the groups (p=0.87). Therefore, there was no indication to undertake further post-hoc paired tests.[2]

5.8.2.2 Correlation of change score of SARA and BARS of scales

The correlation of the change scores of the scales was determined using Spearman's rank correlation coefficient to determine the relationship between the change score of the SARA and BARS, the SARA and PEDI-m, and the BARS and the PEDI-m. The SARA change score demonstrated a moderate correlation with the BARS change score (r=0.64). There was no correlation with either the SARA or BARS change score and the PEDI-m change score (r=-0.06 and r=0.10 respectively).

[2] The responsiveness of the PEDI has previously been reported, with an overall change score of 11% determined to be clinically meaningful (Iyer et al. 2003). This paper was used to complete additional analysis for the SARA, BARS and PEDI data from this study for further information and is presented in Appendix 9.
The global clinical impression of ataxia (i.e. no, mild, moderate or severe) compared with global clinical impression of change is also presented in Appendix 9 for further information, illustrating the need to consider baseline severity of ataxia when determining clinically important difference.

The change scores of the SARA and BARS are also plotted in Figure 5.5.

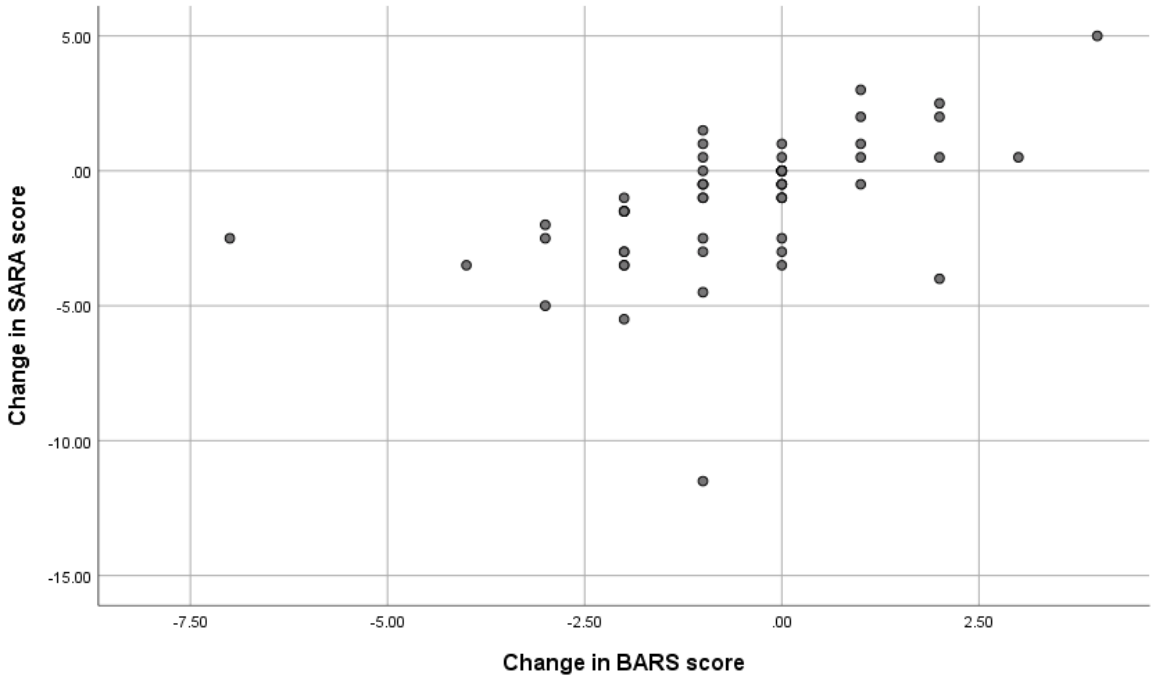


Figure 5.5 Scatter plot, Change in SARA score v Change in BARS score

5.8.2.3 Construct Approach – Hypothesis testing

Hypothesis testing – comparison between subgroups

The participants were split into two subgroups; the acute cohort assessed longitudinally where there would be expected clinical change in the first year post operatively, and the 'stable' cohort who were assessed two or more years post operatively where minimal change is expected.

Hypothesis testing (Wilcoxon signed rank test) was carried out to assess for any difference between the assessment time points for the two sub-groups. The null hypothesis was that there would be no difference between assessment time points at 0 and 3 months, and 3 and 12 months. The experimental hypothesis was that there would be significant change between assessment time points at 0 and 3 months, and 3 and 12 months. However, it was expected there would be no significant change for assessments completed after 12 months.

For assessments at 0 and 3 months the null hypothesis was rejected indicating there was a significant difference in scores between assessments for both SARA and BARS ($p<0.001$ SARA and BARS, $p=0.014$ respectively). For assessments between 3 and 12 months there was a significant difference in the SARA score ($p=0.014$) however, there was no significant difference in the BARS score ($p=0.59$). For assessments at 12 months and 24 months the null hypothesis was retained for both the SARA and BARS ($p=0.312$ SARA and $p=0.28$ BARS) indicating there was no evidence of significant difference between in scores.

For assessments carried out in the 'stable' cohort of participants who were 2 years or more following surgery the null hypothesis was rejected indicating there was a significant difference in scores for the SARA ($p=0.0013$) between their assessments (typically a year apart). However, for the BARS, the null hypothesis was retained and there was no significant difference in BARS scores ($p=0.177$).

Hypothesis testing – before and after intervention

Twenty-five children who were assessed longitudinally from the point of surgery also had a pre-operative assessment carried out (using the SARA scale only). The median pre-operative score was 5 (range 0-24, IQR 7, the median post-operative score was 7.5 (range 0-35.5, IQR 8.22). It is expected clinically that children can demonstrate obvious clinical change between these two time points therefore, hypothesis testing (Wilcoxon signed rank test) was carried out to assess for any difference between these two assessments. The null hypothesis was that there would be no difference between pre- and post-operative SARA scores. The results demonstrated a significance of $p=0.007$, therefore the null hypothesis was rejected suggesting there was a difference between pre- and post-operative scores.

5.8.2.4 Patterns of change - 'acute' participants n=30

Children were assessed at baseline (within one week of surgery), then at the following post-operative times; 3 months, 1 year, 2 years, 3 years and 5 years. Some children continue to be assessed as part of this process depending upon time of recruitment. Descriptive data

of the outcome measures completed is presented in Table 5.11. It is acknowledged that both SARA and BARS scores change over time with age until the adult 'optimum' score of 0 is reached (10 for the SARA and 11 for the BARS, Brandsma et al. 2014). Fifteen children were under the age of 10 years in this group; however, due to the small numbers in the groups it was not possible to consider age as a formal confounding factor in the analysis. Therefore, results need to be carefully considered to ensure any reduction in ataxia score is not related to the child maturing during the study period. Further descriptive data regarding the influence of age are presented in Appendix 9. The reduction in ataxia scale score between initial post-operative and 3-month assessment is above that which would be expected for a change in age.

Table 5.11 Longitudinal Cohort, Outcome measures, n=30

	Baseline n=30	3 months n=27 (3 missing)	1-year n=28 (1 missing, 1 RIP)	2 years n=26 (2 missing, 2 RIP)	3 years n=24 (2 RIP, 1 withdrew (progression, 1 over 18, 1 missing, 2 awaiting assessment)
SARA Median Range IQR	 8.75 0-35.5 9	 5 1-30 3.5	 3 0-28.5 6.25	 2.75 0-16.5 6	 1.75 0-17.5 6
BARS Median Range IQR	 7 0-25 11	 3 0-24 3	 3 0-24 5	 2 0-16 5	 1 0-14 3
PEDI-m Median Range IQR	 57.3 15.2-100 30.45	 89.2 25.4-100 20.2	 94.2 30.6-100 20.2	 100 47-100 17.5	 100 53.1-100 5.8

The change over time was plotted for each outcome measure up to 3 years post-operative and is presented in Figures 5.6, 5.7 and 5.8. A rapid drop in both SARA and BARS mean scores is noted from baseline to 3 months followed by a minimal change at 1, 2- and 3-years post-operative. A reduction in SARA/BARS score represents improvement in ataxia. Four children (out of 30) demonstrated a reduction in SARA score of more than 2 points

after 2 years post-operatively. The graphs for both the SARA and BARS reflect the trend that would be expected to be seen clinically.

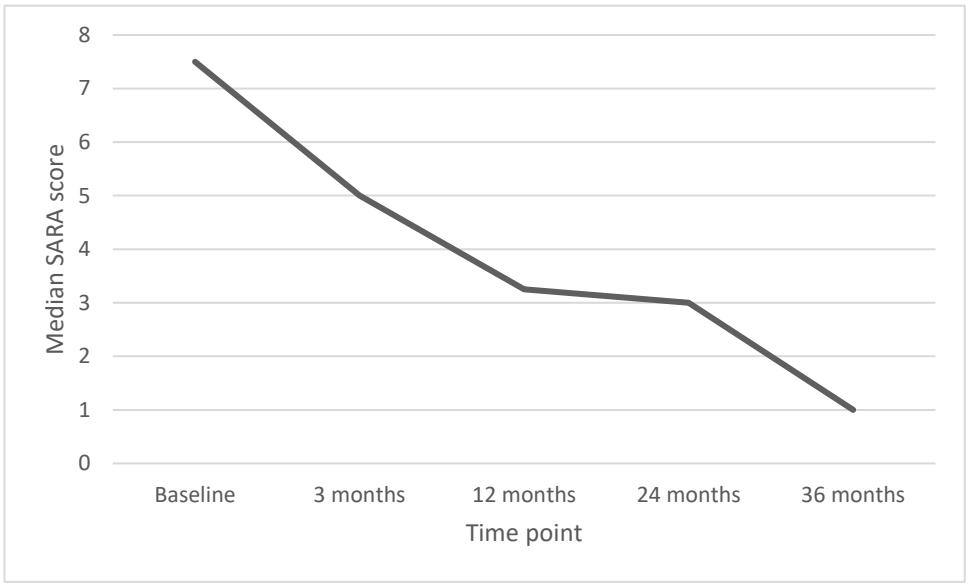


Figure 5.6 Change over time of median SARA total scores for participants assessed up to 3 years postoperatively (plotted for participants with complete set of outcome measures)

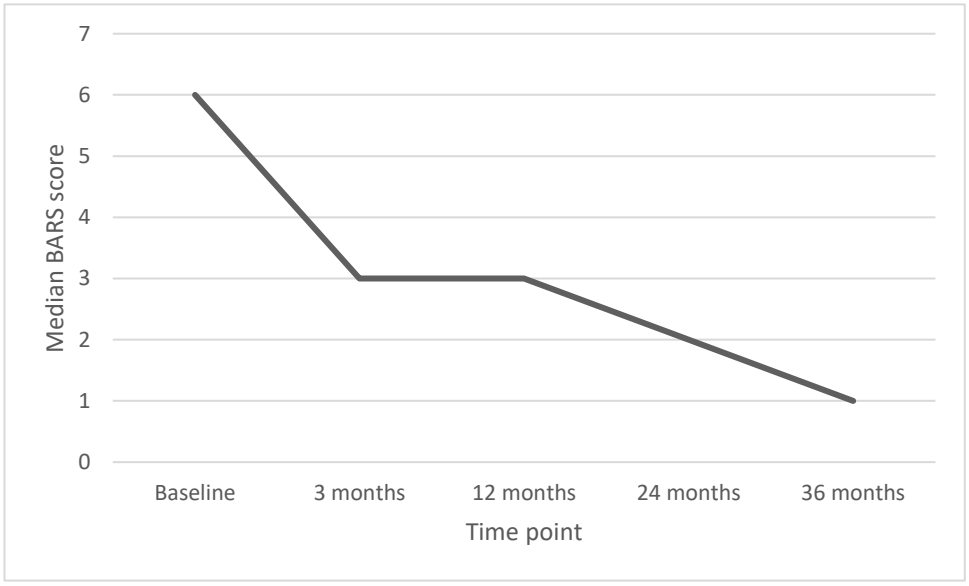


Figure 5.7 Change over time of median BARS total scores for participants assessed up to 3 years postoperatively (plotted for participants with complete set of outcome measures)

The graph illustrating change in BARS (figure 5.7) demonstrates a similar trajectory to the graph illustrating change in SARA indicating consistency in change for the two scales.

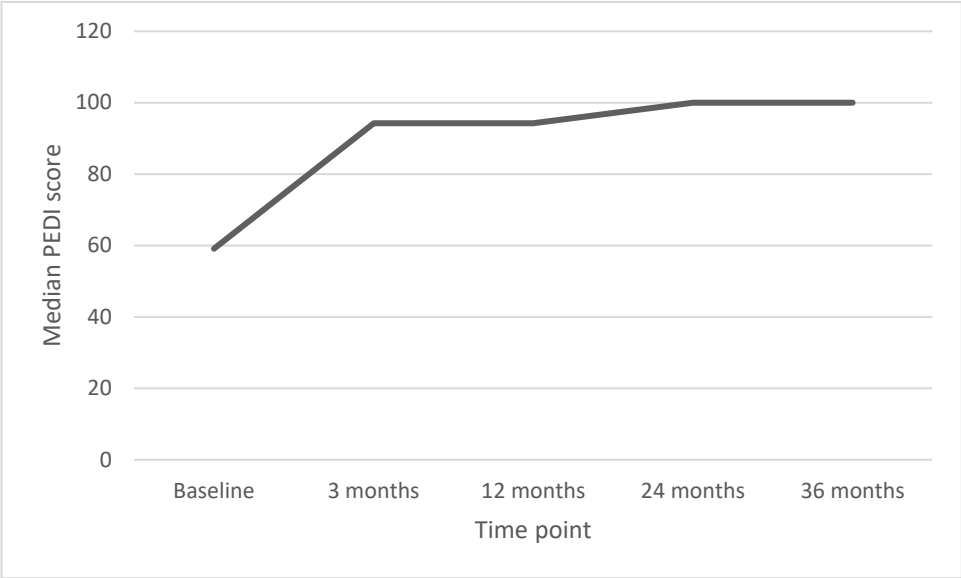


Figure 5.8 Change over time ofmedian PEDI-m total scores for participants assessed up to 3 years (plotted for participants with complete set of outcome measures)

The graphical representation of the PEDI-m (Figure 5.8) demonstrates a significant increase in score (which represents improvement in function) between 0 and 3 months and minimal change at 1, 2 and 3 years postoperatively. This is what would be expected clinically with this population group.

5.8.3 Longitudinal nature of ataxia considering tumour type and location; acute participants

Further analysis was completed for the acute participants (n=30), to illustrate change in outcome measure score dependent on tumour histology (medulloblastoma versus low grade glioma) and is illustrated in Figures 5.9, 5.10 and 5.11.

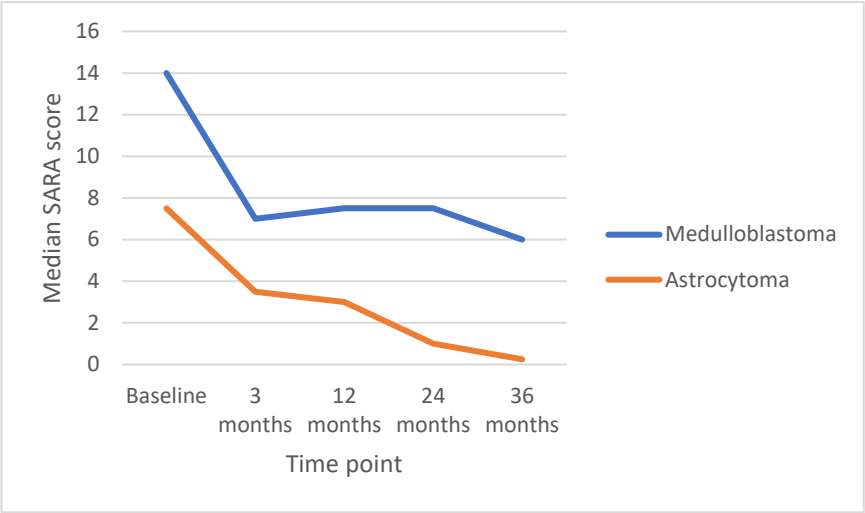


Figure 5. 9 Change over time of SARA score dependent upon tumour histology

Figure 5.9 illustrates that although children with both tumour types follow a similar trajectory, i.e. rapid drop in ataxia from baseline to 3 months post-operatively, children with medulloblastoma present with higher SARA scores (worse ataxia) than children with low grade glioma (LGG, predominantly pilocytic astrocytoma). However, for children with medulloblastoma, there is less improvement after the 3-month assessment time-point. This would be expected clinically that children with medulloblastoma typically present with more balance and coordination problems due to the need for adjuvant therapy and known increased risk of CMS. The SARA score appears to be able to distinguish between the two tumour types.

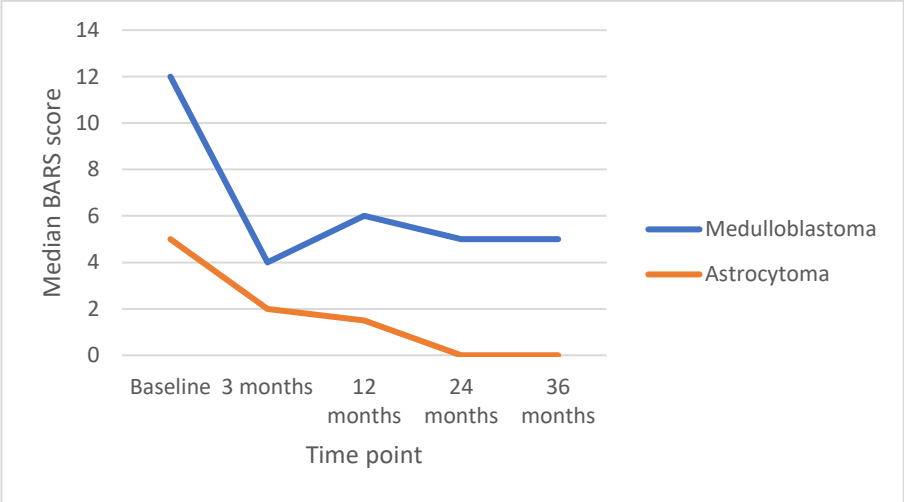


Figure 5. 10 Change over time of BARS scores dependent upon tumour histology

Figure 5.10 illustrating change in BARS scores, demonstrates a similar trajectory to SARA scores, with children diagnosed with a medulloblastoma presenting with higher BARS (i.e. more ataxia) which again is what would be expected clinically. The BARS appears to be able to distinguish between tumour types. It is noted Year 1 assessment BARS scores are slightly higher (2 points) than 3-month assessment scores for children with medulloblastoma.

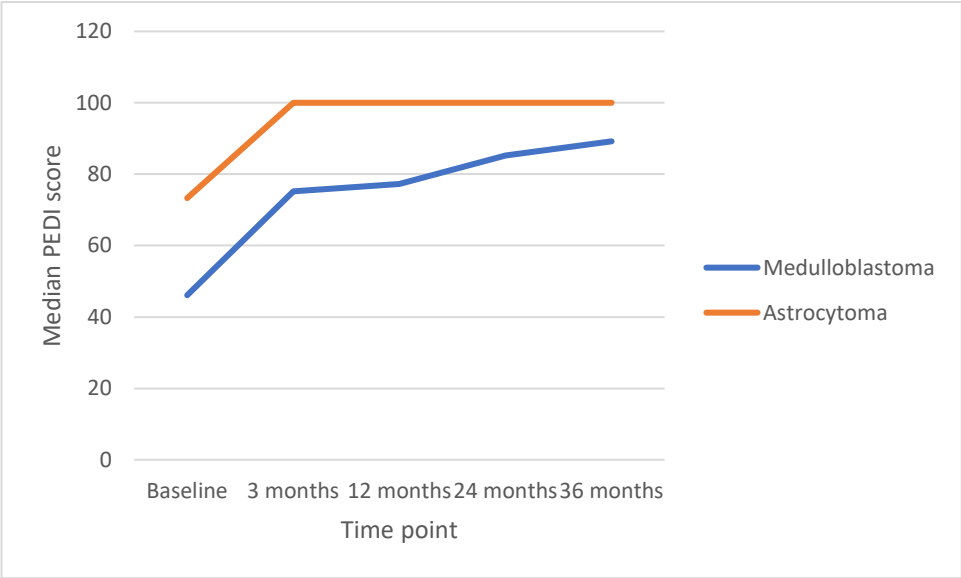


Figure 5.11 Change over time of PEDI-m scores dependent upon tumour histology

Figure 5.11 illustrates children with LGG have consistently higher PEDI mobility domain scores than children with medulloblastoma, this is what would be expected clinically.

Further analysis was completed to compare change over time for outcome measure dependent on tumour location and this is presented in Figures 5.12, 5.13 and 5.14.

Figure 5. 12 Change over time of SARA scores dependent upon tumour location

Figure 5.12 illustrates that children with unilateral located tumours continue to improve over the assessment time points whereas children with midline tumours showed a rapid improvement from baseline to 3 months as previously reported, with smaller change up to three years post-operatively. There is a clear gap at 2- and 3-years post-surgery between the two tumour locations.

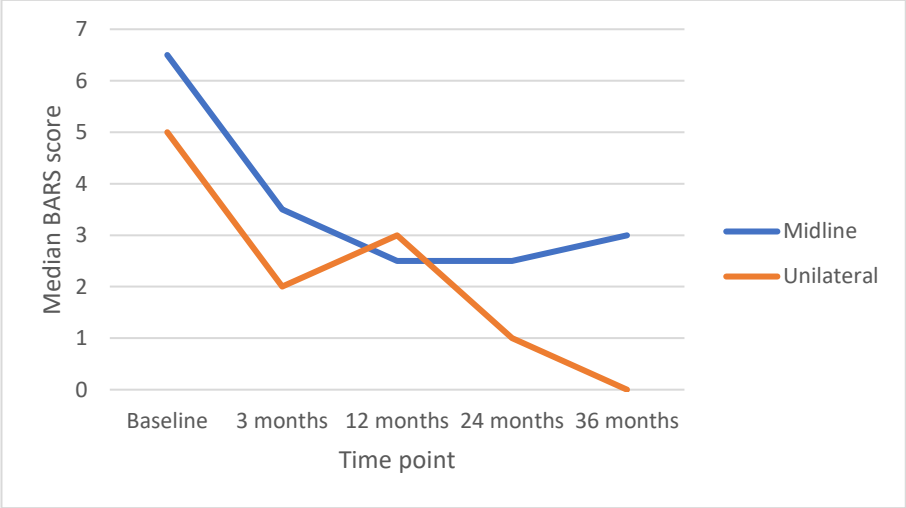


Figure 5.13 Change over time of BARS scores dependent upon tumour location

For children with midline tumours the change in BARS scores are consistent with change in SARA score, i.e. a rapid change between baseline and 3 months post operatively and

then a small amount of change to 3 years post-operatively. Children with unilateral tumours demonstrated ongoing improvement in BARS score (similar to the SARA score) however, there is a small increase in BARS (by 1 point) at the 12-month assessment. Again, children with unilateral tumours present with lower ataxia scores as would be clinically expected. The gap widens after the 24-month time frame with the BARS score appearing to detect a difference with tumour location (Figure 5.13).

Figure 5. 14 Change over time of PEDI-m scores dependent upon tumour location

Figure 5.14 illustrating change in PEDI-m scores demonstrates the same trajectory as previous, with a rapid increase in scores between baseline and 3 months although there is less difference in scores between tumour location.

5.8.4 Summary of the results

Overall, both the SARA and the BARS ataxia scores appear to reflect change over time. The SARA may have the potential to be more sensitive to subtle change. The SARA and BARS scores for children assessed longitudinally from the time of surgery demonstrate the trend that would be clinically expected with the most change occurring in the first 3 months

post-operatively, although there does appear to be potential for improvement in some children even after 2 years following surgery.

5.9 Discussion

The aim of this chapter was to examine the SARA and BARS scales with particular reference to responsiveness and change over time to assist with the selection of an ataxia scale as an outcome measure in the feasibility RCT. This is the first time that the responsiveness of the SARA and BARS has been explored in any paediatric population.

5.9.1 Synthesis of results

The initial CARS study demonstrated that both the SARA and the BARS were feasible to administer and provided evidence of inter-rater reliability, low measurement error and construct validity in children with PFT. Rater feedback about ease of interpretation was slightly stronger for the SARA although the BARS was quicker to carry out (average 2.7 minutes compared with average of 4.5 minutes for the SARA). The correlation coefficient (Pearson's) to reflect reliability was high for both scales (0.94 SARA, 0.91 BARS). Good correlation with the PEDI was observed in cross sectional data (-0.77 SARA, -0.76 BARS) illustrating that higher (worse) ataxia scores were associated with lower (worse) physical function. (The initial CARS results are summarised in Appendix 7).

Further analysis, completed for this PhD programme of work, was undertaken on the assessments of 78 children who had entered the CARS study between 2012 and 2017 providing a larger cohort for analysis. The participant characteristics were reflective of the population managed at the tertiary centre. The range and median scores of the SARA, BARS, and PEDI-m of the study population indicated that most children were demonstrating mild ataxia and physical function problems which is reflected in previous analysis and in keeping with other literature (Hartley et al. 2018, Piscione et al. 2014, Bonfield & Steinbok 2015).

5.9.2 Cut off values

Cut off values of severity of ataxia were calculated from the whole cohort of 78 participants. The cut off value for distinguishing no ataxia from mild ataxia was 1.75 on the SARA (in clinical practice this would be a score of 2). This is similar to the adult literature where a score of 2 or under was typically thought to represent no ataxia (Schmitz-Husch et al. 2006). However, it should be remembered that children do not reach their adult optimum score of '0' on the SARA score until the age of 10. Therefore, it might be expected that the threshold for no to mild ataxia would be higher in children. However, when the specific data for the 78 participants is considered, only 5 children considered by raters to have no ataxia were aged 10 or under, and the lowest age of children with no ataxia was 8. This might explain why the cut off values are similar to those in the adult population. However, this could be conversely interpreted as a concern that raters interpreted higher scores as ataxia when they in fact this could be within 'normal limits'. Although when individual scores are examined further, it is noted that 13 children under the age of 10 were thought to have 'moderate or severe' ataxia and their scores ranged from 5.5 to 22 (median for 'moderate' 12, median for 'severe' 19.5). This is higher than the highest values reported in healthy children for their age (Lawerman et al. 2017a) and adds weight to the raters being able to determine ataxia from age related maturation of coordination skills. However, due to known increased variability in scores for younger children caution should be applied in interpreting these cut off values for this age group.

5.9.3 Floor/ceiling effects

No floor or ceiling effects were demonstrated with the SARA or BARS from the baseline assessments of the whole cohort of 78 participants. However, 14 out of the 78 (18%) participants reached the maximum available score on the mobility domain of the PEDI (PEDI-m) at baseline assessment. It has been suggested that ceiling effects are present if over 15% of participants achieve the highest possible score (Terwee et al. 2007). It is also acknowledged this analysis was carried out on baseline assessments and the ceiling effect

may be larger at subsequent assessment time points (e.g. 1 year or 2 years post-operatively) when children are expected to improve. This raises concerns about using the PEDI-m in this population group for children with milder problems, although there are currently limited alternative choices validated for children with brain tumours. Therefore, it may be of value to evaluate the caregiver assistance and modifications section of the PEDI, as although the overall mobility score might have remained the same, the amount of assistance the child needs to complete this might have reduced which could be meaningful for the child and family. An alternative option would be to use the PEDI-CAT, an electronic version of the PEDI which is in use (Haley et al. 2005) and has now been validated in the inpatient and post-acute setting in children and young people aged 2-21 years of age (Dumas et al. 2015, Fragala-Pinkham et al. 2016). The PEDI-CAT is now being used in a small number of centres across the UK, potentially restricted by the licence costs which require regular updated and software arrangements to allow it to be used on NHS secure computers at the patient's bedside.

PEDI is the only physical function measure currently formally validated in children with acquired brain injuries although it is noted that other measures (e.g. Bruininks-Osteretsky test of Motor Proficiency 2 (BOT-2) (Deitz et al. 2007)) have been used in studies with children with traumatic brain injury (Dahl & Emanuelson 2013) and also with posterior fossa tumours (Piscione et al. 2014), although not validated in these population groups specifically. The BOT-2 was developed for use in children with developmental coordination disorders although it does have the advantage of having norm referenced values available. Other commonly used measures in clinical practice (and other rehabilitation studies) are the 6-minute walk test (6MWT) (ATSCoPSfCPF 2002) or 10 metre walk test (Collen et al. 1990, Watson et al. 2002, Bohannon 1997) and timed up and go (TUG) (Shumway-Cook et al. 2000, Steffen et al. 2002). Although they do not provide as much detail as the PEDI (which e.g. includes items regarding getting in/out of a bath, indoor and outdoor mobility, and stairs) they are simple to use measures and could continue to show progression later

post-operatively. The 6MWT has been validated in adults with TBI (Mossberg 2003) and has normative data for children (Geiger et al. 2007). The 10-metre walk test has again been examined in adults with TBI (Tyson & Connell 2009) and children with neuromuscular disorders (Pirpiris et al. 2003), normative data has also recently been explored (Periera et al. 2016). The correlation between the TUG and the SARA scale has also been reported in adults with cerebellar ataxia (Winser et al. 2017). It should be remembered that in the initial post-operative period some severely affected children might not be mobile at all, and therefore could not complete the alternative outcome measures suggested (BOT-2, 10 metre walk test, 6MWT), thus, the PEDI-m was chosen as it has flexibility to show progression for children with significant difficulties although potential ceiling effects should be considered.

5.9.4 Responsiveness

Responsiveness, as previously stated, is the ability of the outcome measure to detect change over time in the construct to be measured (measure of longitudinal validity) (Terwee et al. 2007). However, debate continues over the best method to examine this e.g. as a range of different approaches exist including consensus-based approach, distribution-based methods and anchor-based methods. There appears to be a move away from distribution based methods and the COSMIN guidelines state that effect size and standardised response mean, and paired t tests are inappropriate methods to examine responsiveness, with concerns that these may reflect magnitude of change due to an intervention rather than the quality of an outcome measure (Mokkink et al. 2010a). Distribution based methods also rely on statistical and psychometric properties of a measure in a specific population (Perera et al. 2006). COSMIN recommendations suggest anchor-based methods (utilising clinician impression of change) which consider the change scores against a related concept (e.g. change score on comparator instrument) are more appropriate (Mokkink et al 2010a, b), as these can be used to compare change in each direction and based on clinical perception of change. However, it is often difficult to

implement these as typically there is no gold standard outcome measure to use as a comparator to look at change score. It is suggested though that hypothesis testing, e.g. about expected correlations in measures or expected differences in changes between groups, is a relevant method (Terwee et al. 2007, Mokkink et al. 2018a). Anchor-based and hypothesis testing were therefore included in this data analysis alongside additional analysis which was appropriate to the data. Further, anchor-based analysis (with the use of multiple anchors) would be of value in a larger sample group, e.g., previously mentioned functional outcome measures such as the TUG or 6MWT could be used as alternative anchors. An alternative option could be to use a measure of health state, e.g. understanding the wider ranging impact of ataxia on the child's health as reported by the child/their family (Madans & Webster 2015). It may also be beneficial to consider the relationship between the SARA and BARS and measures of sway, e.g. wearable trunk accelerometery or more formal measures incorporating balance platforms. This could further illustrate the relationship of ataxia scales with related constructs. Other options would be to consider the association between the scales and specific balance outcome measures, e.g. the Berg Balance Scale (Berg et al. 1992) or Paediatric Balance Scale (Franjoine et al. 2010).

The responsiveness of the SARA has been examined in adults with spinocerebellar ataxia (Schmitz-Hubsch et al. 2010). This was determined in response to the patient's global impression (similar to principles used in this study where the clinician impression of change was used), although Schmitz-Hubsch et al. (2010) also used the standardised response mean, which as noted above is not currently recommended as an appropriate method.

The SARA and the BARS both appeared to reflect change in children with PFT with the data analysed. With specific respect to the analysis of scales against clinician impression of change, the data suggested that the SARA may be more sensitive to subtle change and the SARA scale demonstrated the trend that would be expected, with sequential drop in score from minimally better to much better. However, it is observed that there were only

very small numbers for analysis in the subgroups, and it would be of value to explore this further with larger participant numbers, particularly as baseline severity of ataxia might be important, e.g. a child with mild ataxia has a limited potential to change in ataxia score. Therefore, having a larger dataset and being able to look at change in groups from different baseline severity would also be of interest.

One main outlier was noted in the data when examining responsiveness. A child had been reported as being worse by the clinician despite a lower SARA score. The BARS score increased by two (in keeping with potential deterioration) although the PEDI-m increased which again would not be expected, although this was under the MCID reported for the PEDI. Therefore, this case was reviewed further, and it was noted that this participant presented with significant treatment-related side effects which affected their functional ability and quality of life. This may have affected the clinician's (and family's) perception of their presentation although their ataxia was not necessarily accounting for their difficulties at that time. It can be challenging for both the clinicians and parents to consider ataxia in isolation when other components may be influencing the child's motor skills. The challenge with using the GCI-C has been more extensively reported in adult mental health research with consideration that other factors may influence clinicians' perceptions (Busner et al. 2009). This raises the difficulty of using GCI as an anchor (particularly as it was the single anchor used) as although the clinician is typically judging the impairment, they could potentially be taking into account what is happening with the rest of the child's presentation.

Although there was a moderate correlation between the SARA and BARS change score (r=0.63) there was no correlation between either the SARA or BARS change score and the PEDI-m change score. Neither was there a strong link between GCI-change and PEDI change. This is unexpected as there was a good correlation between single cross-sectional scores of the SARA and BARS with the PEDI-m in the original CARS study. This may again be influenced by the ceiling effect of the PEDI-m and, as discussed previously, it might be

therefore of value to consider other elements such as change in caregiver assistance. If this analysis was repeated in a larger data set it would be beneficial to remove those participants from analysis who were at the ceiling as they are unable to progress further.

Overall, although the SARA and BARS scores did follow the trend of a drop in score linked with perceived clinical improvement judged by clinicians, it would also be of value to consider parental perceived change as, in practice, parents sometimes report a positive change in ataxia where the child may be compensating and there is no actual change in severity of ataxia (although they may have achieved functional goals though this compensatory approach).

From the data a MCID was suggested (+/-2 for both the SARA and the BARS), though this should be interpreted with caution, as it was calculated from low numbers and is based on statistical significance only. However, the MCID for the SARA in adults has been examined in a large dataset (171 adults with genetic ataxia) with a difference of 1.1 reported as being clinically important (Schmitz-Hubsch et al. 2010). The MCID would be expected to be higher in children where there can be increased variability in performance (particularly in the younger age group) therefore the MCID suggested in this study appears an appropriate starting point. A threshold of two (or more) was also suggested by Lawerman et al. (2017a) to allow for inter-individual variability in maturation following consideration of their normative data on healthy children, thus corroborating the data in this study. Fatigue changes within the course of the day may influence variability in score and therefore it seems reasonable a change of more than one is required to represent a clinically important difference. The next step would be for clinicians to verify the MCID in practice, and if a large sample size is available, it may also be important to consider the baseline severity of ataxia when reporting the MCID (e.g. it might be thought that a greater reduction in SARA scale is required to perceive a meaningful change if baseline severity is high). The perception of change may be related to the percentage change in score rather than a score reduction.

When reviewing hypothesis testing between subgroups, results typically followed clinical expectations with significant changes in the baseline to 3-month assessment timepoint, however between 3- and 1-year post operatively only the SARA demonstrated a significant change. This could be because the SARA is more weighted towards the 'midline' gait, stance, and sitting scores which have more potential for improvement compared to the BARS which is more focused on kinetic domains and eye movements. Eye movements can remain abnormal not just because of cerebellar problems but due to the effects of hydrocephalus and other eye movement disorders. There was no significant difference in the SARA or BARS for assessment at 1 year and 2 years post-operatively which would be as expected, as clinical change typically slows later following surgery. However, in the 'stable' group of 36 children who were 2 years or more following surgery there was a significant difference in SARA score (but not BARS) between their assessments. Considering the raw data descriptively, 12 of the children were observed to have a drop in SARA score of more than 2 points. This is not expected and therefore should be examined further in a larger dataset to check and see if this can be corroborated. There could be true improvement in some children (e.g. children who have improved following completion of chemotherapy, or those who have attended specialist centres for rehabilitation), and it would be of interest to examine characteristics of children who do have the potential to improve in the longer term. The BARS may not detect a change as it is not as focused on balance and has other anatomical features such as eye movements which are not as likely to improve as much.

Hypothesis testing in the data analysis did include examination of pre- and post-operative SARA scores, as this is a time point when clinically obvious change is often seen. However, although the results supported clinical expectations and are of clinical interest, in essence, this analysis strictly only examines the effect of surgery and any implications regarding the validation of the SARA should be interpreted with caution. From a clinical perspective if would be of interest to see if children go back down below their pre surgery SARA score in

the longer term. This could be examined in a larger dataset and corroborated by larger studies (e.g. the NORDIC CMS study).

5.9.5 Longitudinal nature of ataxia

Whilst initially aiming to explore responsiveness for the SARA and the BARS the results also provide information regarding the natural history of ataxia in children following surgical resection of posterior fossa tumour. The baseline scores following surgery are in keeping with results from a multicentre Italian study (Panzeri et al. 2020), who reported a median SARA of 8.3 (rising to 14.5 if other clinical signs present), compared with a median SARA baseline of 8.75 in this study, adding confidence to the results. The most rapid period of change (improvement) was noted in the first 3 months post-operatively, with much smaller change (a continued positive trend albeit not consistently significant) up to 3 years post-operatively. This trend was reflected in the scores for the PEDI-m where a rapid improvement was noted at the 3-month assessment followed by minimal change after this point. Due to the small numbers in this study when examining subgroup data, although it is known that SARA scores are age dependent in healthy children (Brandsma et al. 2014, Lawerman et al. 2017a), it was not possible to consider age formally as a confounding factor in the analysis. However, it should be noted that although children may not reach the adult optimum for the SARA (and BARS) scores until the age of 10, recent information (Lawerman et al. 2017a) suggests that median scores in healthy children from age 6 to 10 years are under 1.5 and show only small changes of 0.5 for each age group. Therefore, this would suggest that significant changes seen in the first 3 months following surgery are consistent with recovery and repair of brain function and not just age-related maturational changes. Descriptive preliminary analysis of the SARA utilising normative data from the European Study (Lawerman et al. 2017a) presented in Appendix 9, suggests that there is a reduction in ataxia between the 3 month and 1 year post-operative assessment in eight to eleven year olds that is not explained by maturational changes (but not after 1 year post operatively). There is also a reduction in children over the age of eleven changes at all three assessment

time points, again which cannot be explained by maturational changes though the small numbers in these subgroups according to age is acknowledged. These finding suggest there is potential for recovery distinct from age related maturation although it is more difficult to identify this in younger children as the variability in rate of maturation in younger children is higher.

This pattern of change is supported by the longitudinal study by Kuper et al. (2013), which measured function in 12 children (age range 6-17 years of age) who were followed up to one-year postoperatively. They observed a reduction in ataxia score (using the ICARS) from acute testing to 1 year follow up, with a statistically different score from acute to 3 months, but not from 3 months to 1 year, similar to findings from this study. They did observe an improvement between 3 months and 1 year with alternative outcome measures using balance testing (body sway tested using motion analysis) and upper limb motor function. Kuper et al. (2013) suggested that reduction in oedema affecting the deep cerebellar nuclei was a predictor of early functional recovery. It might be thought that resolution of oedema would happen over days to weeks (Xu et al. 2014), and therefore it would be of interest to see at what point recovery slows. E.g., inclusion of an assessment time point at one-month (in addition to the three-month assessment) may indicate whether there is a time of most rapid change (improvement) that corresponds with resolution of oedema. If this is not evident, it would be interesting to consider the mechanisms underlying recovery in the acute phase.

The recovery trajectory identified in the present study is also reflected in studies of children with acquired brain injury (from other pathologies) where the most rapid change occurs in the first 6 months post neurological insult, although there is potential for change further post injury in some cases (Kelly et al. 2014).

The ongoing multicentre cerebellar mutism syndrome (CMS) study (NCT02300766) may provide further information about the trajectory of ataxia. The CMS study includes

assessment time points as follows; pre-operative, initial post-operative, 2 months, and 1-year post-operative using the BARS (and other more detailed speech assessments). It would be useful to see if the CMS study confirms the findings of this Phase of the ASPECT study, though it is noted that again only one year follow up is undertaken in the CMS study. This Phase of the PhD programme is therefore the first study to report ataxia and physical function outcomes up to three years postoperatively.

Children with medulloblastoma and midline tumours typically demonstrated consistently higher ataxia scores (and lower physical function scores) throughout the trajectory of their recovery. This is in line with other studies reporting that children with medulloblastoma have a higher incidence of ataxia and cerebellar mutism syndrome (DiRocco et al. 2010, Robertson et al. 2006, Cochrane et al. 1994, Bull et al. 2014). By contrast, children with low grade gliomas (LGG) (predominantly pilocytic astrocytomas) typically demonstrated lower ataxia scores with the mean ataxia score at three years being under the threshold of 2 for no ataxia. These findings are further supported by research that reports children with LGG will, most often, have mild cerebellar dysfunction (Bonfield & Steinbok 2015). This may be due to a typically more lateralised tumour location or no requirement for adjuvant treatment. However, it should be considered that there are risks associated with surgery and the incidence of long-term neurological impairment for children with LGG is wide ranging (11-47%) (Aarsen et al. (2005) (47% motor impairment), Steinbok et al. (2013) (16% long term neurological deficit), Zuzak et al. (2008) (43% neurological impairment, Ait Khelifa-Gallois et al. (2014) (11% significant neurological sequelae)).

It is therefore difficult to determine the influence of tumour histology compared with tumour location on ataxia severity, as there is an inherent link between the two factors; medulloblastoma more often being midline than lateralised in the cerebellum and LGG showing the converse relationship. To further investigate this issue a new study (outside this PhD programme, with myself as CI) which uses medical imaging to investigate the

relationship between tumour histology, location and ataxia severity is underway. It has previously been observed that lesions to the deep cerebellar nuclei and inferior vermis have been linked with persistent motor deficit in children (Konczak et al. 2005, Puget et al. 2009). The new study will therefore also compare specific tumour location and cerebellar volume in relation to ataxia scores. It might also be of interest to look at the Bal-SARA subscores (as described in more detail below) particularly in relation to location of tumour as this subscale may be more sensitive to midline cerebellar lesions than the standard SARA scale.

Other elements in addition to tumour location and histology should be considered, the most obvious being the need for adjuvant oncology treatment i.e. radiotherapy and chemotherapy for children with medulloblastomas. Indeed, it is noted that peripheral neuropathy which is a known side effect of chemotherapy can impair postural control strategies and result in functional balance problems (Horak et al. 1997). To understand this further, it would be of value to explore the specific impact of adjuvant therapy with a larger dataset, e.g., to look at the trajectory of ataxia severity in children who had surgery alone compared to those who had surgery and radiotherapy, and those who had surgery and chemotherapy (ensuring that any extra-cerebellar and peripheral neuropathy signs are part of the assessment process).

It was also noted that the difference in severity of ataxia scores dependent on tumour histology was wide at initial baseline, then became closer at 3 months, then widened again, with children with medulloblastoma continuing to present with more severe ataxia at 3 years (and with less potential for improvement after 3 months post-operatively (Figures 5.9, 5.10). Additionally, a plateau in PEDI-m scores was noted for children diagnosed with medulloblastoma following their 3-month assessment, again potentially reflecting that these children undergo intense adjuvant oncology treatment involving radiotherapy and chemotherapy which can also impact on physical presentation (Piscione et al. 2014). For children with medulloblastoma, dependent upon risk group, surgery is followed by 6 weeks

of radiotherapy which commences around 4 weeks post-surgery and this is then followed by a long course of chemotherapy. The optimum timing of rehabilitation should therefore also be considered carefully for children who have been treated with adjuvant therapy.

In the future it would also be of interest to illustrate the trajectory of children with different ataxia severity, e.g. to consider the pattern of change for children with severe ataxia over time compared with children with mild/moderate ataxia to consider if there is any difference in recovery. This analysis was not completed due to small numbers of children in the severe group. Mapping individual trajectories might also be of value to identify characteristics of participants who do show potential for ongoing improvement to see if this can inform practice.

5.9.6 Choice of scale between SARA and BARS

Both scales appear to measure change in the severity of ataxia in children with PFT. It was noted that the SARA may be more sensitive to subtle change and if this is demonstrated in a larger dataset then this would strengthen the case for using SARA in clinical trials. From the previous CARS work both scales demonstrated good inter-rater reliability and construct validity. It is noted the BARS is quicker to carry out, but the rater feedback from the original CARS study was more positive for the SARA scale. As the preliminary analysis did not provide compelling evidence that one scale was better than another, both scales were therefore used in the feasibility RCT (Phase 4). Using both the SARA and BARS in the feasibility trial also offered the possibility of exploring the psychometric properties of these scales in more detail.

It should be considered that the SARA and BARS scales treat the link between anatomy and score differently. The SARA score takes the average between the left and right limbs, implicitly assuming that ataxia presents symmetrically on both sides of the body. The BARS takes the sum of both sides, which does not make a significant difference to the total score but could have an influence when correlating individual lateralised items with factors such

as lateralised cerebellar anatomical changes on MRI. This may indicate that the BARS is of value in the acute surgical population where the specific location of the cerebellar lesion may be influential, whereas the SARA was designed for use in the genetic ataxia population who are more likely to have bilateral symmetrical changes. Due to the difference in the content of the scales and the way items are measured it is of value to use both scales in the feasibility RCT as this will provide more data to potentially consider the impact of the difference in weighting of the scales.

Another difference in the scales is the inclusion of an eye movement item in the BARS, with less importance placed on the balance and posture related measures. The BARS may therefore be less sensitive to balance changes but could potentially highlight the oculomotor aspects of vestibulocerebellum problems (as eye movement issues are thought to be related to damage to part of the vestibulocerebellum (Manto & Marien 2015). Although there have been concerns regarding reliability of this item, and an eye movement item was removed from the SARA due to its effect on reducing internal consistency. The BARS score for children with midline tumours may be higher than those with unilateral tumours as there is the clinical potential to have eye movement problems with midline tumours but the correlation between the SARA and BARS was very high (Appendix 7) and there was no evidence that the scales were different in different populations (e.g. tumour location). This may be due to the fact that there is only a 2-point item for eye movements in the BARS so this might not be sensitive enough to highlight specific lesion-based issues. In the future with a larger data set it may be possible to calculate an equation that could convert the SARA to the BARS which may be of use to compare studies that might have used single scales, but this would be interpreted with caution as it would only apply to the specific population it had been calculated for.

Both the SARA and BARS reflect a marker of composite ataxia impairment, but additionally, there have been studies that have specifically focused on three items of the SARA (gait,

stance and sitting) and claim this modified version specifically measures balance deficits. This has been referred to as the Bal-SARA (Bunn et al. 2015), SARA-Bal (Winser et al. 2017) and SARA [Gait/Posture] Lawerman et al. 2017b). These balance components have been drawn out with the thought that if balance is the specific focus of a study (e.g. intervention based study focused on balance as the primary outcome) it would be more relevant to look at change in the Bal-SARA, than the overall score as it would be unlikely that other items e.g. upper limb kinetic accuracy may change. The Bal-SARA has been shown to be reliable and valid to use in adults with cerebellar ataxia with fair responsiveness for the gait and sitting items (Winser et al. 2015), with a minimal detectable change suggested as 2 (Winser et al. 2017). The Bal-SARA is also very short and therefore might be more suitable for younger children. Indeed, it is reported that there is less variation in the Bal-SARA (compared with the full SARA) in younger children (Lawerman et al. 2017b) again highlighting its potential benefit. Additionally, there is an indication of a relationship between the Bal-SARA and measures of sway (Bunn et al. 2013) and examining this further in children with PFT would be of value. This may add weight to using the SARA in further intervention trials (such as Phase 4 of this programme of work) as subscales such as the Bal-SARA can be pulled out and analysed further.

5.9.7 Limitations

The main limitation for this study is the small sample size which is particularly relevant when subgroup analysis was completed, although the only previous similar study (Kuper et al. 2013) followed 12 children, therefore this study (which included 78 children, 30 followed longitudinally) provides an advance on this. Ongoing data collection (not part of work reported in this PhD) will result in additional participant data and assessments that could be considered at a later date to check if trends seen in the initial analysis are confirmed with a larger data set. Despite a small sample size, this study is the first to assess ataxia for up to 3 years post-operatively and is the largest longitudinal study to focus specifically on ataxia in this population group.

Additionally, the lack of a validated gold standard outcome measure to compare the scales with was a challenge. This problem is often seen in rehabilitation research and the data analysis was therefore adapted accordingly using clinician perceived change as an appropriate marker. Earlier in the discussion the challenge of using GCI change was examined as, in individual children, judgements of wider aspects of disability might influence opinion rather than specific ataxia impairment. It is also important to acknowledge that although the GCI is a recognised way of recording change in healthcare (Busner & Targum 2017), it was designed for use in the field of psychology, and it has not been examined formally in children with ataxia. The PEDI-m was also chosen as a related construct (and a relationship between the scales and the PEDI-m had been demonstrated in the original CARS study). However, the PEDI-m did not appear to be as useful in longitudinal assessment in this population group; this may have been influenced by a ceiling effect. This meant that only a single anchor was used in the anchor-based method (the GCI-change) whereas multiple anchors would have been of benefit. It should also be acknowledged that ataxia is a composite construct and although balance and eye movement items (and resulting deficits) have been discussed when considering the differences between the two scales, it may also be of value to consider the speech or upper limb elements (e.g. through use of upper limb validated measures) as tumour location could influence deficits in certain components of ataxia which may be of interest.

This Phase of the programme of work along with the CARS study has evaluated inter-rater reliability, construct validity and responsiveness although not all domains of measurement property have been examined for the scales and therefore these should be completed in the future. A classical approach to psychometric analysis was used in this phase of the study, although other models such as Rasch analysis are becoming increasingly used in health outcome measures (Sandham et al. 2019). Further data on the SARA and BARS scales could benefit from this approach where the focus is on the individual item level (i.e. the response to a particular item can be affected by the characteristics of the person and

the characteristics of the item) and identifying and eliminating any sources of item bias leading to improvement in reliability and validity of a measure (Ashford et al. 2016). A Rasch converted interval scale would help address the issue with the limitation of MCID in ordinal scales. As the points are not equally distributed in the SARA and BARS there will be some inherent error in determining a degree of change which can be accepted as real change at any point along the ordinal scale.

5.9.8 Dissemination and future research

Interim results for Phase 1 of this programme of work were summarised and presented by myself to ISPNO 2018 (International Symposium on Paediatric Neuro Oncology) as a poster. These data were then used as a basis for a presentation to the Posterior Fossa Society (August 2018, presented by myself) and European Paediatric Neurology Society Research Meeting (October 2018, presentation delivered by Dr Ram Kumar). Further analysis was presented at the British Paediatric Neurology Association (BPNA) Neuro-Oncology Rehabilitation Study day (March 2020, presented by myself), and British Paediatric Neurology Association Movement Disorders Special Interest Group (May 2020, presented by Dr Ram Kumar) both of which generated discussion on the use of outcome measures in this population group. Discussion between the research team and the professional audience included the challenges of assessment of children under the age of 5 and the trajectory of improvement in children with posterior fossa tumours. Other discussions included the development of the BARS and the potential for adaptation of a paediatric version of the BARS. Phase 1 data was also accepted for oral presentation at ESPN (European Society for Pediatric Neurosurgery) 2020, however, this was delayed due to COVID-19.

Future research (outside of this PhD programme, with myself continuing as CI) has also been instigated to examine any links with ataxia and other difficulties commonly found in children with PFT; eye movement problems, audio-vestibular dysfunction, and neuro-psychology deficits. Approval has also been sought to explore MRI images in relation to

ataxia scores with specific respect to cerebellar volume. A research ethics amendment to the original CARS protocol has been approved by the REC. Children previously recruited to the CARS study are being approached for re-consent where appropriate and the study is now re-open again to recruitment of new participants. Collaboration with the radiology, audio vestibular, ophthalmology, and neuro-psychology team will enable review of these data in the future. There has also been discussion with the CMS study team regarding future examination of ataxia as part of a collaborative approach with the CMS team, and there is opportunity to validate the findings of this study with the larger international study data.

5.10 Conclusion

Overall, there is evidence that both the SARA and BARS scales reflect change in ataxia, which provides initial support to utilising these scales in clinical practice and future research. There is the suggestion that the SARA may be more sensitive to subtle change, although the small numbers considered in this subgroup analysis mean this finding should be interpreted with caution.

A MCID of +/-2 is suggested based on this study's findings, although the difficulty of interpreting a meaningful change in ordinal scales is acknowledged and further research would be of benefit to validate this result.

The results provide useful information about the course of ataxia in children who have had surgical resection for PFT and consolidates reports in the literature that children with medulloblastoma and midline tumours present with more balance and coordination problems. The most rapid change was seen in the first 3 months postoperatively (which appears to be clinically meaningful) followed by a small change up to 3 years postoperatively. Any later changes do not appear to be explained simply by developmental maturation of cerebellar function especially in adolescents, though the impact of age should be examined further. Overall, this suggests a potential use for the scales as an outcome measure for guiding neurosurgical strategy in PFT.

Overall, the findings would benefit from further confirmation with a larger data set, but they do demonstrate the need to consider the effectiveness of targeted rehabilitation intervention in the later stages post-operatively when children typically appear to demonstrate minimal change.

Chapter 6 - Phase 2 – e-Survey of current international physiotherapy practice for children with ataxia following surgical resection of posterior fossa tumour

6.1 Introduction

The knowledge gap regarding physiotherapy intervention for children with ataxia has been established in Chapter 3, and in particular, there is a lack of literature on physiotherapy treatment for children who present with ataxia following surgical resection of a posterior fossa tumour (PFT). Despite the lack of evidence to guide best practice, it is recognized that physiotherapy is integral to the treatment of children with neurological deficits following management of a brain tumour (NICE 2005), yet details regarding current physiotherapy practice are not known. Understanding current practice could aid development of clinical guidelines and assist with the planning of clinical trials in this population. To gain an understanding of physiotherapy treatment for this population group across different countries an e-survey was developed to scope current practice. An e-survey is an efficient method of collecting data from a broad spectrum of individuals and different settings (Kelley et al. 2003). The rationale underpinning the development of the e-survey was informed by searching and reviewing examples of questionnaires in relevant literature, and discussion papers together with literature on survey/questionnaire design. These elements informed the research question and the content, structure, and sampling frame of the e-survey. The scope of the e-survey was deliberately widened to add breadth and additional information on the challenges to rehabilitation in children with PFT.

6.2 Research question

What is current international practice and what are the challenges to physiotherapy management for children with posterior fossa tumours?

6.3 Aim

The aim of this study was to determine current international practice regarding physiotherapy input for children with ataxia following surgical resection of posterior fossa tumour, and to understand the specific difficulties physiotherapists face when working with this population group.

6.4 Specific objectives

The objectives of this study (Phase 2) were to:

1) Gain an increased understanding of current international physiotherapy practice in relation to treatment methods by
    - identifying the most frequent physiotherapy treatment methods used;
    - identifying the most frequent adjuncts to treatment used;
2) understand the challenges to rehabilitation in children with PFT;
3) explore physiotherapists' views of the benefits and challenges of using virtual training in this population group;
4) generate an understanding of the range of the dosage of physiotherapy treatment (duration, frequency, intensity), and timing of treatment; and
5) inform the subsequent phases of the larger study, in particular the rationale underpinning the feasibility RCT in relation to intervention parameters such as timing and intensity of treatment.

6.5 Study design

A survey was chosen to answer the research question as it provided a cost-effective way to collect a broad range of data (Kelley et al. 2003) which was required in this instance to meet all the specified objectives. An e-survey was selected as this offered an efficient method of reaching a range of respondents across different countries. Additionally, the special interest groups were contactable via email and use this method to communicate with their members, which again directed towards the use of an e-survey. An e-survey also facilitated the possibility of snowballing recruitment (where existing participants recruit future respondents from their acquaintances) (Eysenback & Wyatt 2002). Using an e-survey means that the initial results are instantly available, and they can be easily exported to facilitate subsequent analysis. Problems with surveys include factors that may impact on data analysis (Ponto 2015) these may result from respondents interpreting questions differently, not providing accurate responses and not responding to questions. The e-survey was anonymized to encourage open responses from respondents about their practice. The piloting process helped to minimize these known limitations of surveys (Mathers et al. 2007).

6.6 Summary plan of investigation

The key points of the study included:

1. Development of the e-survey;
2. piloting the e-survey;
3. refinement with feedback from pilot;
4. dissemination of the e-survey to the target population;
5. reminder to the target population;
6. analysis of results; and

7. dissemination to respondents and wider audience with interest in neuro-oncology.

6.7 E-Survey development

A literature search identified no previous surveys on this topic that could be used for this study (Phase 2). Therefore, the e-survey was purposefully designed to ensure the specific objectives of this study were met. To assist with the development of this data collection tool the initial search was widened to source examples of similar surveys scoping therapy practice, firstly in relevant conditions, and then extended to include examples of scoping practice in paediatric physiotherapy across any condition. The searches did not identify any surveys that explored physiotherapy practice for children or adults with brain tumours although there was an example sourced on exercise in cancer care (O'Hanlon & Kennedy 2014) which was useful as background information in a closely related area. In particular the grouping of questions into sections such as professional profile, exercise in cancer care and prescription of exercise, provided reference for possible groups of questions. There were also examples of questions on intensity of intervention (in this case exercise) which provided examples of question wording. However, it was noted that some questions had multiple parts and were more difficult to understand which helped to direct the need for conciseness of questions for this study. Sections of this e-survey were also informed by previous surveys which examined scope of paediatric physiotherapy practice in neurodevelopmental follow up (Harniess & Nikopoulou-Smyrni 2015) and lower limb amputee rehabilitation (Treby & Main 2007). These surveys had similarly grouped questions beginning with respondent characteristics and moved on to more specific questions to match the target objectives.

Following the literature search in this area, the sections of the e-survey were confirmed by a method of consensus within the supervisory team which included myself as a specialist

clinician in this area, two other physiotherapists with expertise in ataxia, two consultants with an interest in this clinical field (Paediatric Oncologist and Paediatric Neurologist) and a professor of children's nursing with experience of surveys in paediatric healthcare. The sections were determined to ensure that the content reflected the objectives of the survey which included gathering views on types of intervention, intensity and timing, and also specific feedback on virtual training. These were linked to the last objective that was to inform subsequent planning of the RCT for Phase 4 of the PhD programme.

SurveyMonkey® (SurveyMonkey Inc, USA, www.surveymonkey.com), an online survey development cloud-based software company, was chosen as an electronic method of delivering the survey as access to this was available via the research team. It is a popular online survey method and enables the use of logic to build and direct participants through the survey and results can be directly exported into Excel (Microsoft ® Excel) to enable analysis.

The appearance of the survey was considered as this is potentially important to increase response/completion rate (McColl et al. 2001). There was consistency in presentation of visual information and spatial arrangement to assist respondents to navigate through the questions as easily as possible. Questions were clearly numbered and grouped by subject into different sections as further described below, again for ease of completion (Kelley et al. 2003). The wording of questions was carefully considered to ensure the language used was as clear as possible, and understandable to people with English as a second language which was of particular importance in view of an international audience for the survey. Questions were kept as short as possible and asked for only one piece of information at a time to promote clarity (Leung 2001). A mix of closed and open questions was used, with the acknowledgement that open questions although allowing more freedom of responses lead to a longer completion time and potentially a wide variety of responses. Therefore, open questions were carefully placed where responses were not likely to fit a pre-

determined selection of responses and where more depth and a greater understanding of individual therapists' thoughts were beneficial to meet the specified objectives. The summary structure of the e-survey is presented below in Table 6.1.

Table 6.1- Structure of e-survey

Section	Title	Exemplar Content	Question Type
	Introduction	E.g. aims and information on confidentiality	1 filter question tick box.
Section One	Demographics	E.g. location of workplace, qualification, years post qualification, number of children with brain tumours treated per year	8 multiple choice tick box questions. 3 short answer questions.
Section Two	Treatment and Intervention	E.g. type of therapy intervention used most frequently and adjuncts to therapy	7 multiple choice tick box questions.
Section Three	Virtual Training	E.g. benefits/challenges of using virtual training in this population group	1 multiple choice tick box question. 1 multiple choice with option for short answer. 3 open questions.
Section Four	Intensity and Timing	E.g. length of physiotherapy sessions, and dosage	6 multiple choice tick box questions.
Section Five	Aims and Outcomes	E.g. common aims of therapy, challenges and outcome measures used	3 multiple choice tick box questions. 5 open ended questions.

An introductory section included a clear statement of aims and information on confidentiality/how the data would be handled to enable the participants to make an informed decision to take part or not (this was in accordance with HRA (2017) guidance for applying a proportionate approach to the process of seeking consent). It also made clear that the e-survey was anonymous. The wording of this section was carefully chosen, e.g. using the terms physiotherapist and physical therapist (acknowledging the varying terminology in different countries) to reflect the international audience.

The draft e-survey began with an initial filter question checking that respondents were physiotherapists working with children with posterior fossa tumours to ensure this inclusion criterion was met. If the respondent selected 'no' to the filter question, they were directed to

an automatic response that thanked them for their interest but ended their participation in the e-survey.

Section one contained 11 questions on background information from respondents; it is typical practice for surveys to begin with such general questions (Mathers et al. 2007). Nine of these questions were closed questions which have the advantage of being easy and quick to complete by the respondent and are also simpler to code and subsequently record results (Leung 2001). For the closed questions the answers were defined in advance and respondents were limited to one of the pre-coded responses given. The choice of answers was carefully considered to cover the whole spectrum of possible responses from physiotherapists. Tick box responses were used throughout the survey for closed questions (and partially coded open questions) to ensure consistency and further ease completion.

Section 2 focused on intervention type and adjuncts to treatment (defined as another treatment used together with a primary treatment aiming to assist the primary treatment to meet the specified aims) and consisted of seven questions. The physiotherapists were first asked to select which interventions they used from a pre-determined list. The list was developed in conjunction with the supervisory team and informed by relevant literature discussing physiotherapy interventions in children with cerebral palsy. This literature came from other surveys (Saleh et al. 2008) and systematic literature searches on interventions for children with cerebral palsy (Dewar et al. 2015, Anttila et al. 2008) to ensure the choice was comprehensive. However, the questions on interventions also allowed an option of 'other, please specify' to catch any responses which might not have been thought of before. The pre-selected list of interventions also included definitions of each therapy type to ensure that all participants had a good understanding of what was meant by each type of intervention. After selecting all interventions they might use, the respondents were then asked to choose which intervention they used most often, and finally they were asked to rank which three interventions they thought were the most effective. A number of different

questions were asked about type of intervention used to ensure the topic was fully covered and check there were no inconsistencies in responses. A similar process was followed for questions on adjuncts to treatment, with a predetermined list compiled with the supervisory team and informed by literature in the cerebral palsy field (Dewar et al. 2015, Anttila et al. 2008). Definitions were provided to ensure clarity and ease of understanding. Respondents were asked the three same questions; indicate which adjuncts to treatment you use in practice, what is the adjunct to treatment you use most often and rank your top three most effective adjuncts to treatment. This section ended with two closed questions to allow respondents to indicate whether they based their intervention on any clinical guidelines or research evidence.

Section 3 focused on virtual training (defined as the use of computer technologies that provide an interactive environment requiring limb movement to react to on screen game play (Vernadakis et al. 2014)) and consisted of two closed and three open questions. This section helped to inform subsequent phases of the PhD programme. It opened with a general closed question to determine if the therapists had used virtual training in their overall physiotherapy practice. If the respondents had used virtual training they were directed to a further question on which population they had used this in. A partially coded open-ended question was used for this, with the pre-determined list of populations informed by pathologies which have been examined using virtual training to date in the literature and allowing an 'other' option for respondents to specify if they had used this in practice for other types of patients. They were then asked for further information on the top three benefits and then challenges they had found using virtual training in their practice. If they had not used virtual training they were automatically directed to a question enquiring why, with options such as limitations/barriers. The subsequent questions were open-ended to allow further exploration on this topic which was of importance to direct Phases 3 and 4 of the study.

Section 4 was designed to scope variability of responses concerned with timing and intensity of treatment to determine what might be considered a standard or typical dose. The results of which informed the protocol of Phase 4 of the study. It consisted of six closed questions (although the last question in this section allowed for additional comments to support whether the respondents felt that physiotherapy was optimally timed). There was less variability in possible responses regarding timing and intensity of treatment therefore closed questions were chosen for these questions. Creating a predetermined choice of answers regarding timing and dosage of physiotherapy intervention (e.g. treatment time <30 minutes, 30-<45 minutes) also aimed to allow easier data analysis and reporting (Boynton & Greenhalgh 2004).

The final section focused on aims and outcomes of treatment and consisted of 3 closed and 5 open questions. The closed questions explored typical aims of physiotherapy and reasons for discharge with a selection of pre-determined options available which were generated in discussion with the supervisory team and informed by relevant surveys exploring practice in children with cerebral palsy (Saleh et al. 2008). The open-ended questions allowed exploration of particular areas in more depth including factors taken into account for goal setting and problems with transition. In particular, to inform Phase 4 of the study, participants were asked about challenges to physiotherapy treatment in this population group, with the knowledge that a number of issues could be raised in this area which would allow further thematic analysis.

6.8 Piloting process

Piloting is essential to examine the clarity and acceptability of the survey (Fitzpatrick 1991) and optimize face and content validity and reliability (Harniess & Nikopoulou-Smyrni 2015). Initial testing was done within the supervisory team (with expertise in this area as previously detailed) to determine the correct settings/logic had been applied to the e-survey. The e-

survey was then piloted with four individual contacts who were known to the supervisory team to have a specific interest in this area and who freely consented to undertaking this role after reading study information and having the chance to ask questions about the role of a pilot participant. The contacts were members of the following special interest groups; one from the Paediatric Oncology Physiotherapy Group (POPs), one from the Association of Paediatric Chartered Physiotherapists (APCP), one affiliated to the European Paediatric Neurology Society (EPNS) and one from the Children's Oncology Group (COG). This selection was purposefully made to ensure the pilot respondents shared similar characteristics with those who would be in the target population for the final survey (Leung 2001). There were two representatives from the UK (an acute physiotherapist and a community-based physiotherapist to ensure the questions were applicable to therapists working in either setting), a representative from Europe (speaking English as a non-first language) and a representative from the USA. This helped to ensure the e-survey was easy to understand and respond to by physiotherapists from different countries and settings. In addition to the main survey the pilot respondents were asked to complete an extra four questions; time taken to complete the survey, clarity of the questions (0-100, with 100 being very clear to understand), identification of any problems answering any of the questions, and any further comments regarding the e-survey. The feedback from the pilot is indicated below (Table 6.2).

Table 6.2 – Pilot e-survey feedback

Pilot participant	Time to complete	Clarity of questions (0 = not clear, 100= completely clear)	Any problems answering questions	Any further comments
1	16-20 minutes	90	No	No
2	0-10 minutes	90	Consider staff who have limited experience in working with posterior fossa patient rehab e.g. transition, school setting integration Questions to include "not applicable at the time" option	Yes

3	11-15 minutes	90	No	No
4	16-20 minutes	90	Found the adjuncts to therapy difficult to answer.	Yes

The feedback from the pilot was broadly positive with the physiotherapists reporting that the questions were easy to interpret/answer. One physiotherapist commented that to enable community therapists to answer all the questions there should be 'not applicable to my setting' added for certain questions and these minor amendments were completed. The comment regarding finding the 'adjuncts to therapy' question difficult to answer was not expanded upon, therefore it was difficult to determine the precise problem. However, further advice regarding this was sought via discussion with three physiotherapists working within the Neurosciences Team at the host Paediatric Tertiary Hospital who did not find any difficulties answering this question and thus no adjustments were made regarding this. The time to complete the e-survey was broadly in line with expectations of between 15-20 minutes and this matched the information given to respondents at the start of the e-survey. Three respondents completed all the questions and one respondent skipped two questions. The variability of answers was also reviewed, all respondents were able to complete the sections on types of intervention and no additional types of intervention to those on the pre-selected lists were identified by the respondents. The answers appeared appropriate to the questions and similar responses were noted in terms of aims and challenges to treatment. Therefore, only the minor changes as discussed above were made to the survey following the pilot process.

6.9 Target population

6.9.1 Inclusion criterion

Physiotherapists/physical therapists who were involved in the assessment and treatment of children with ataxia following surgical resection of PFT.

6.9.2 Identifying the target population

Physiotherapists were chosen solely as the target audience as information specific to physiotherapy practice (and not the wider multi-disciplinary team) was required to inform Phase 4 of the study and answer the specific objectives. It was important that the e-survey reached physiotherapists with an interest in this area who would have the relevant knowledge to complete the questions. In the UK children receive their primary management for a PFT at a tertiary Paediatric Neurosurgical Unit with any subsequent oncology treatment carried out at a tertiary Paediatric Oncology Unit (which may or may not be on the same site), therefore the lead physiotherapists for these units would typically be the most experienced in this field. Hence, the starting point to reach therapists in the UK was via two of the Paediatric Physiotherapy Network groups, as all tertiary units are represented in these networks: the Paediatric Neurosciences Physiotherapists (n=30 approximately) and the Paediatric Oncology Physiotherapists (n=20 approximately). Additionally, to reach any community physiotherapists with an interest in this area (as children are typically referred onto community therapists following discharge home from their tertiary centre) the Association of Paediatric Chartered Physiotherapists (APCP) with a much broader membership (n=2,200 approximately) was chosen as another key contact.

To enable dissemination across key international oncology networks, contacts were used within the supervisory team who were members of International Society of Paediatric Oncology European Brain Tumour Group (SIOP-E-BTG) (board members n=20 approximately across 15 countries, full SIOP membership n=1730), and the Children's Oncology Group (COG) (n=9000 across 200 hospitals throughout Europe, USA, Australia and New Zealand) which includes significant American representation which was a key target. It was important to request snowballing of the e-survey to colleagues to increase the potential number of respondents, especially as it was recognized that the e-survey may initially be sent to physicians/other non-physiotherapy professionals through SIOP and COG (the number of physiotherapists who are members of SIOP or COG is not known).

Therefore, there was an automatic request as part of the e-survey to 'please forward to physiotherapy colleagues with an interest in this area'. Links within the COG group also then led to contact within the Paediatric Physical Therapist Special Interest Group (n=120 approximately) in the USA. The Posterior Fossa Society (PFS) (n=65 approximately) was also another key network selected as it includes representation internationally from health care professionals with a specific interest in posterior fossa tumours (although only three members are physiotherapists). It was known that most members of the PFS are neurosurgeons, oncologists or psychologists, and thus again snowballing was crucial to promote the dissemination of the e-survey to physiotherapy colleagues. To enable the e-survey to reach physiotherapists whose main interest may be ataxia, the survey was also sent to the European Paediatric Neurology Society (EPNS) (n=1,300 approximately) as this society has an ataxia special interest group. This would allow dissemination through paediatric neurology colleagues. The use of both oncology and neurology special interest groups was useful as it is acknowledged that physiotherapists treating children with ataxia following management of a PFT may be classed as specializing in either neurosciences or oncology dependent upon services in that particular country.

The e-survey was therefore sent out to a very large sample of people although it is acknowledged that only a small proportion of the larger special interest groups would be physiotherapists. Overall, the aim was for the survey to reach over 20 countries and over 100 different physiotherapists with a target response rate of 50 respondents from 10 countries to generate meaningful findings.

6.10 Recruitment

The final version of the survey (Appendix 10) was sent to contacts from seven key groups (over 100 centres) via the Paediatric Oncology Physiotherapy Network (POPs group), Paediatric Physiotherapy Acquired Brain Injury Network, APCP (Association of Paediatric

Chartered Physiotherapists), SIOP-Europe Brain Tumour Group with particular engagement of the Quality of Survival Working Group, COG (Children's Oncology Group), PFS (Posterior Fossa Society) and EPNS (European Paediatric Neurology Society). For each of these network groups a gatekeeper (the identified contact for each network e.g. administrator/relevant research lead for the network) sent out an email to the members of the groups on behalf of the research team that contained a link to the survey. Through previous correspondence with members of the groups it was known that many people in the network had good ability to speak English therefore the survey was only offered in English. Engagement with the COG group also led to direct contacts within the Special Interest Group for Physical Therapists working in Paediatric Oncology.

The respondents were given two weeks to respond then a reminder was sent out electronically to aim to increase the rate of response (McColl et al. 2001). A further two weeks were given to respond before preliminary data collation began.

6.11 Ethical issues

Ethical considerations for the study included the process of informed consent, how to approach potential respondents, time burden for respondents, sensitivity of questions and data handling/protection and confidentiality. The survey was granted ethics approval through Edge Hill University FREC committee (FOHSC 170) (See Appendix 11).

Regarding informed consent there was a short introductory page as part of the survey to provide potential respondents with sufficient information to enable them to reach an informed decision whether to complete and return the survey or not. The information described the nature and purpose of the research, why they were invited to take part, and how the information collected would be used. The return of the survey was deemed to be the respondent's consent to participate.

The e-survey was disseminated via gate keepers for each of the identified network groups (following confirmation through the gate keeper or chair of the association that they were happy to disseminate the e-survey). This enabled the gate keepers to contact their members with an email which contained a link to the e-survey and thus no individual email contact was required.

Following the piloting process, a good understanding of the time to complete the e-survey was gained and this information was made clear to respondents on the first page of the e-survey. It was not anticipated that the questions would cause any distress as no questions were deemed to be sensitive. The respondents' responses were anonymous.

6.12 Research governance issues

Data protection and confidentiality issues were also considered. To ensure confidentiality of personal data, no specific personal data was collected at the level that would allow traceability. No personal data was stored or shared. SurveyMonkey® was set so that the researcher did not know the IP address of the respondents and the spreadsheet exported from SurveyMonkey® was password protected. Email addresses for key network contacts/gatekeepers were stored on a secure drive on a NHS computer that was password protected. Only the supervisory team, via the lead researcher had access to anonymised data. Data analysis took place at EHU and the host NHS Foundation Trust.

All due care and attention was paid to the management of the data in line with policies from Edge Hill University and host NHS Foundation Trust. Data will be stored securely for 10 years after the research concludes (in line with the Data Protection Act 1998, now replaced with General Data Protection Regulation GDPR 2018).

The study was monitored by the supervisory team and there was additional external oversight from the NIHR in the form of regular reports on the progress of the study.

6.13 Data analysis

The data were exported from SurveyMonkey® into an Excel spreadsheet for further analysis.

Descriptive statistics (number and percentage of respondents) were used to report the closed questions (demographics of the respondents, most effective interventions/adjuncts, use of virtual training, intensity of treatment and use of outcome measures). Additionally, graphs populated from the Excel spreadsheet were used to provide an illustration of the data about types and frequency of usage of interventions/adjuncts. The approach was predominantly quantitative with embedded qualitative elements designed to offer respondents with the opportunity to clarify or contextualise answers.

The qualitative analysis was informed by a inductive (data led) approach situated in an essentialist framework (reporting the respondents' perceptions and experiences assuming a straight-forward relationship between the written account and the perceptions) (Braun & Clarke 2006a) framed from a physiotherapist perspective. All data from selected open questions were initially transferred from Excel into NVivo to allow the data to be clearly read and re-read to ensure familiarity with the data. Initial codes were then generated before subsequent sorting of codes and where there was evidence of recurring responses, themes were initially developed. The themes were subsequently refined and presented in text and also thematic maps (Braun & Clark 2006b).

6.14 Results

Overall, 140 respondents entered the e-survey, with 120 physiotherapists/physical therapists answering yes to the initial filter question and proceeding to answer the subsequent questions on the e-survey. It was not possible to report a response rate due to the method of disseminating the e-survey and subsequent snowballing as it is not known

how many physiotherapists the e-survey reached in total. The overall completion rate was 41%, with initial questions being answered completely by 96 respondents. Some of the later open-ended questions were answered by fewer respondents (average 60 respondents), although some of these questions were only applicable to certain groups of therapists (e.g. those who had used virtual training). The results of each section of the e-survey are now presented.

6.14.1 Section 1: Demographics

Ninety respondents were female and six were male. The respondents had a range of qualification level with 72 qualified to degree level. Twenty-one (22%) had additional post graduate qualifications including MSc and PhD. All therapists qualified to PhD level were from the UK/Europe: England (n=2), Germany (n=2), France (n=1), The Netherlands (n=1). Further details are presented in Table 6.3.

Table 6.3 Participant baseline information (N=96)

	Number of respondents (%)
Gender	
Male	6 (6)
Female	90 (94)
Qualification	
Diploma	6 (6)
Degree	72 (75)
MSc	14 (15)
PhD	7 (7)
Location	
UK	53 (56)
Rest of Europe	23 (24)
USA/Canada	10 (10)
Australia/New Zealand	10 (10)

Overall, 12 countries were represented with over 50 responses from physiotherapists across the UK (including England, Wales, Scotland and Northern Ireland), with good representation from the rest of Europe. Detailed breakdown of the European response is

presented in Table 6.4. Ten respondents from the USA/Canada and 10 from Australia/New Zealand also completed the survey.

*Table 6.4 - **European representation (n=23)***

Country	Number of respondents
Belgium	1
Germany	2
France	3
Italy	9
Lithuania	1
Netherlands	3
Republic of Ireland	4

The respondents demonstrated a range of experience with the majority (71%) being over 10 years qualified. A range of experience in working with children with brain tumours was reported with 59% of respondents having more than 5 years of experience in this particular field. The median number of children treated per year with PFT was 10 (see Table 6.5).

Table 6.5 Participant experience (N=96)

	Number of respondents (%)
Years Qualified	
0-2	4 (4)
3-5	4 (4)
6-9	20 (21)
>10	68 (71)
Years experience working with children with brain tumours	
0-2	13 (13)
3-5	27 (28)
6-9	17 (18)
>10	39 (41)
Children treated per year with posterior fossa tumours	
Median (range)	10 (0-100)
Skipped question	45 (38)
Post graduate training in working with children with post fossa tumours	
Yes	22 (23)
No	74 (77)

Where respondents indicated they had completed further training the most common type of training was a short course in either ataxia or oncology. Internal in-service training was also reported as a source of training. Three respondents reported they had completed a related MSc module.

The respondents indicated they spent clinical time in more than one workplace location (e.g., a mix of inpatients and outpatients) (Table 6.6). However, the primary work setting of the respondents was an inpatient setting (n=66, 72%) (Table 6.6). This reflects that these children are typically managed in the acute setting in the first instance, and physiotherapists working in specialist neurosurgical/oncology units experience the highest caseload of children with posterior fossa tumours.

Sixty six percent of physiotherapists (n= 61) reported they worked within a specialist team for neuro-oncology. The teams commonly consisted of physiotherapy, occupational therapy, speech and language therapy and nursing staff. Other members of the multidisciplinary team (MDT) mentioned were neuropsychology/neuropsychiatry, radiation oncologist, outreach, dietician, physicians, neurosurgeon, play specialist, sport therapist and music therapist.

Table 6.6 Participant workplace setting (N=92)

	Number of respondents (%)
Work settings (multiple settings possible)	
Inpatient	79 (86)
Outpatient	46 (50)
Clinic	33 (34)
Community	23 (25)
School	17 (18)
Primary work setting	
Inpatient	66 (72)
Outpatient	8 (9)
Clinic	4 (4)
Community	11 (12)
School	3 (3)
Work within specialist team for neuro oncology	
Yes	61 (66)
No	31 (34)

6.14.2 Section 2: Therapy intervention

Respondents selected from a predetermined list of physiotherapy interventions all possible interventions they might use in this population group (selecting more than one possible answer). Seventy-five respondents answered this question. The results indicate that physiotherapists use a range of interventions with balance exercises (n=73, 97%), gait re-education (n=71, 95%), proximal control activities (n=70, 93%), task specific training (n=65, 87%) and strengthening exercises (n=60, 80%) used by the highest number of respondents as illustrated in Figure 6.1. Additional types of treatment reported by the respondents in the 'other' category included coordination activities (n=3, 4%), rebound therapy (n=1, 1%), robotics (n=1, 1%), hippotherapy (n=2, 3%), vocational (n=1, 1%), vojta (involves the therapeutic use of reflex locomotions www.votja.com) (n=1, 1%), gym ball (n=3, 4%) and approximation (compression of a joint) (n=1, 1%).

When asked which intervention type they used *most often*, three intervention types were commonly reported; balance exercises (n=21, 28%), task specific training (n=17 23%) and proximal control activities (n=16, 21%) (Figure 6.2). These three intervention types were also the most frequently ranked in the physiotherapists 'top three' *most effective* types of treatment, with proximal control activities being ranked as the most effective intervention type by 29% (n=22) of respondents who completed that question (Table 6.7).

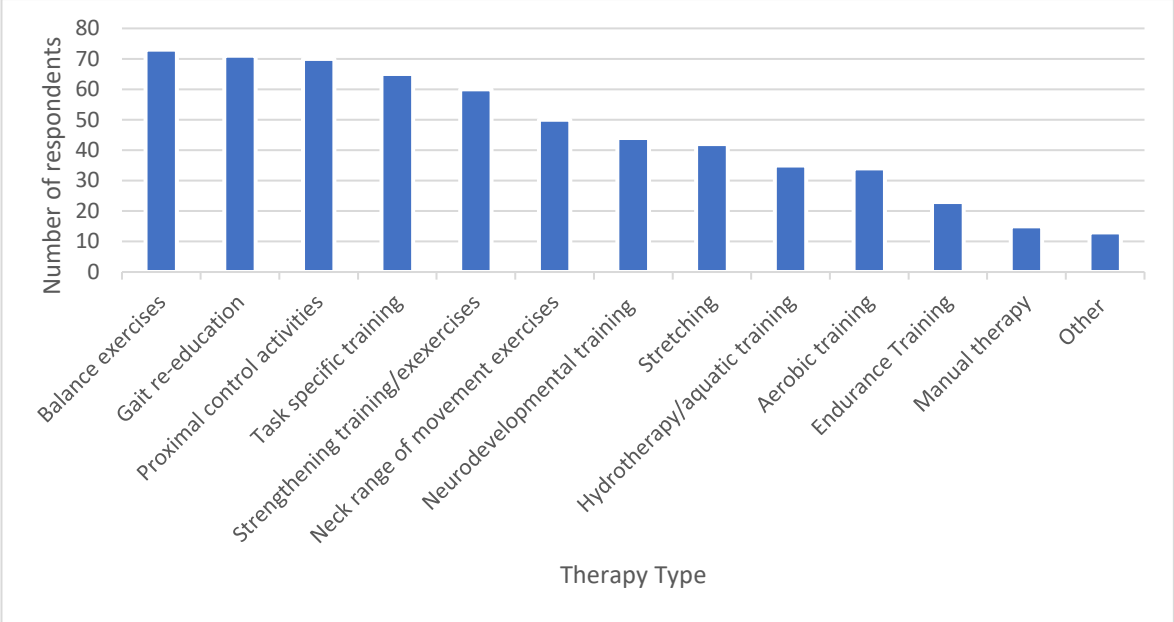


Figure 6.1 – Types of therapy interventions used

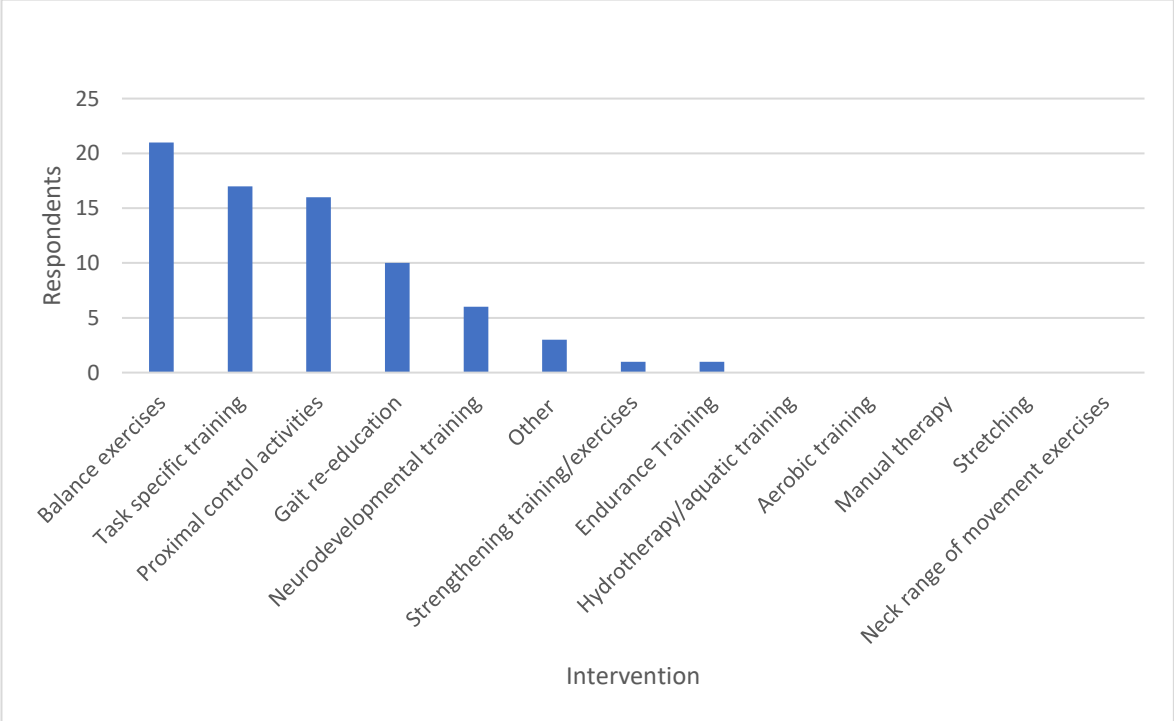


Figure 6.2 - Intervention type used most often

Table 6.7 – Interventions ranked most effective by respondents ordered by the frequency of respondents providing the intervention with a 1st ranking (All respondents asked to select top 3)

Intervention	**Ranked 1st (Frequency)**	**Ranked 2nd (Frequency)**	**Ranked 3rd (Frequency)**	**Total 1-3 ranking (Frequency)**
Proximal control activities	22	13	8	43
Balance exercises	17	18	12	47
Task specific training	15	16	13	44
Gait re-education	9	9	15	33
Strengthening training/exercises	2	7	9	18
Neurodevelopmental Training (NDT)	6	1	4	11
Hydrotherapy/aquatic training	1	3	6	10
Stretching	1	2	0	3
Neck range of movement exercises	0	1	3	4
Endurance training	0	1	0	1
Other (combined approach, unable to say individual to child)	0	1	0	1
Aerobic training	0	0	2	2
Manual therapy	0	0	0	0

Comparison of intervention: UK versus rest of Europe

The intervention the respondents used the most often were also compared between the two largest cohorts in terms of geographical location of respondents (UK compared with the rest of Europe) and are presented below (Figure 6.3). Although the graph demonstrates that balance exercises were popular in both groups (UK n=9, 22%, Europe n=7, 47%), the most commonly used intervention amongst UK physiotherapists was proximal control activities (n=13, 32%). However, it is acknowledged that the European group is a considerably smaller group of respondents compared with the UK group.

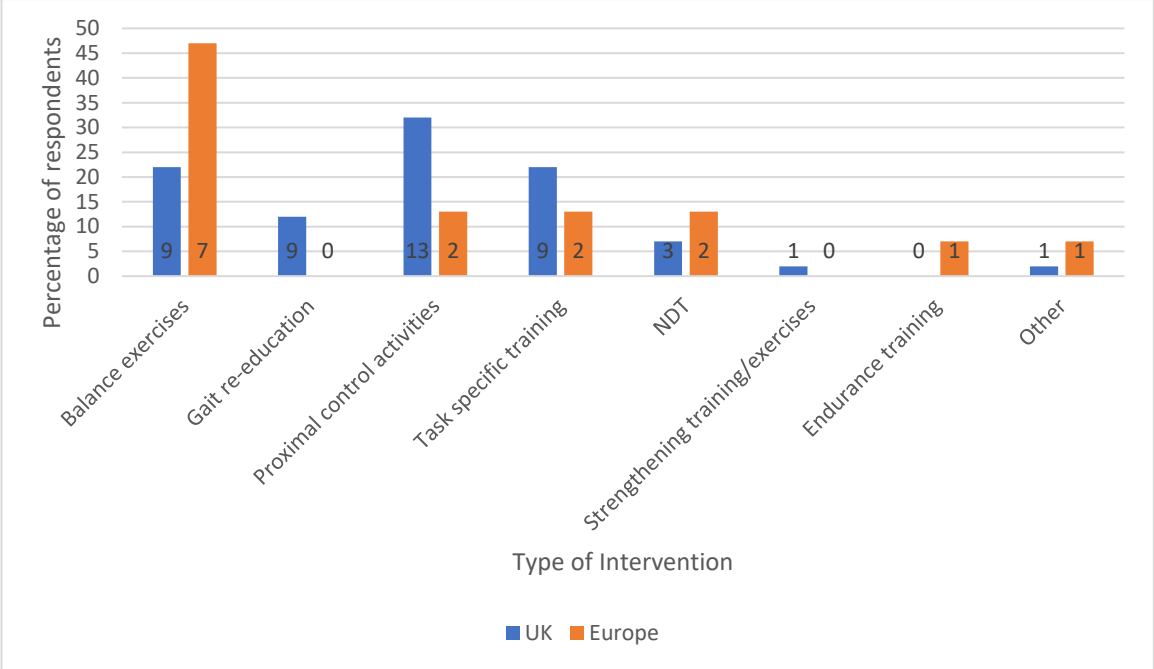


Figure 6.3 – UK versus Rest of Europe response – most commonly used intervention (percentage of respondents reported, with raw numbers as labels)

Respondents then selected from a predetermined list of 'adjuncts to therapy' which types they used in this population group (multiple responses possible). The results indicate that physiotherapists use a range of adjuncts with orthotics (n=61, 82%), walking/mobility aids (n=60, 81%), taping (n=37, 50%), lycra garments (n=32, 43%) and treadmill training (n=28, 38%) used the most frequently as illustrated in Figure 6.4. Another type of treatment proposed by the respondents was gym ball activities. Orthotics (n=23, 31%) and walking/mobility aids (n=23, 31%) were the two adjuncts that were reported to be used most often (Figure 6.5). These two adjuncts to physiotherapy were also the most frequently ranked in the physiotherapists' 'top three' most effective types of treatment (receiving the most amount of first and second choices), though weighted therapy was also popular in this sample with n=10, 14% of respondents, rating this as their second most effective adjunct to treatment (Table 6.8).

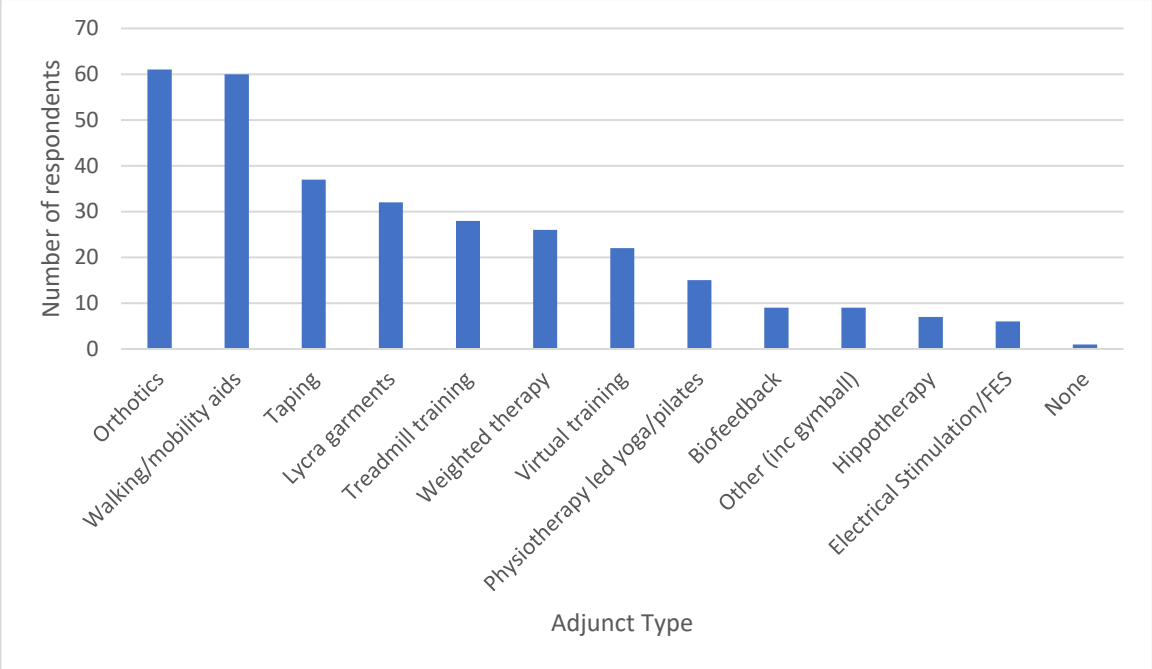


Figure 6.4 – Types of adjunct to therapy used

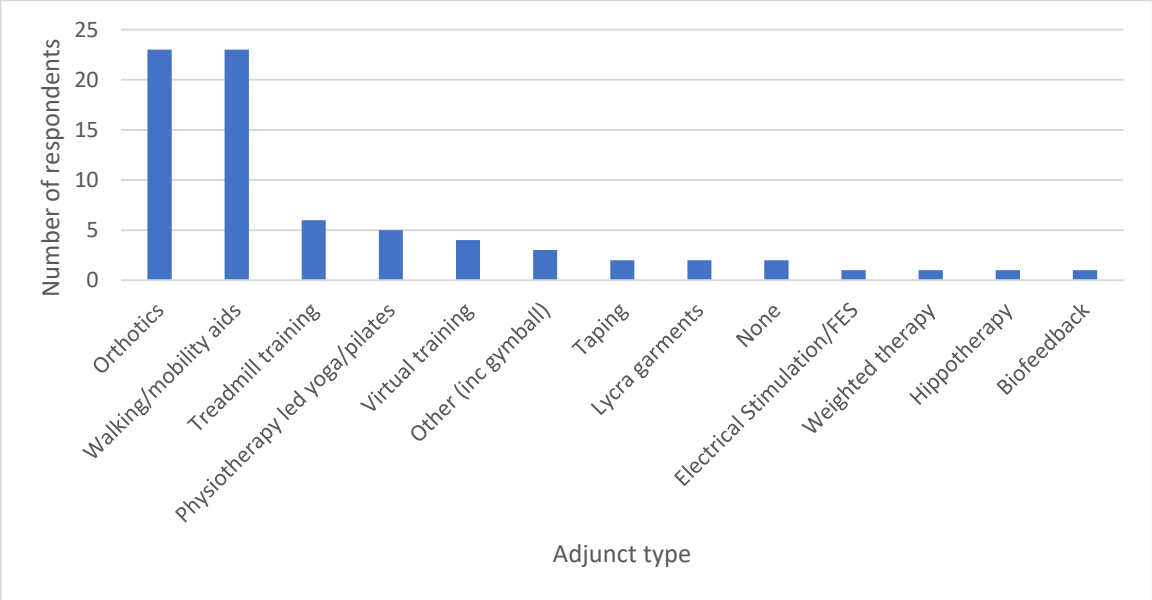


Figure 6.5 – Adjunct used most often

Table 6.8 – Adjuncts to therapy ranked most effective by respondents ordered by the frequency of respondents providing the intervention with a 1st ranking (asked to select top 3)

Intervention	Ranked 1st (Frequency)	Ranked 1st (Frequency)	Ranked 3rd (Frequency)	Total 1-3 Ranking (Frequency)
Orthotics	25	12	12	49
Walking/mobility aids	20	11	16	47
Treadmill training	6	6	7	19
Physiotherapy led yoga/Pilates	4	6	2	12
Lycra garments	3	4	4	11
Virtual training	3	3	6	12
None	3	0	0	3
Taping	2	8	6	16
Weighted therapy	2	10	1	13
Other (including gym ball)	2	1	1	4
Hippotherapy	1	1	2	4
Biofeedback	1	1	4	6
Electrical Stimulation/FES	0	1	0	1

Respondents were also asked whether they based their intervention on any clinical guidelines specific to the treatment of children with PFT. Only 8% (n=6) reported using guidelines, highlighting the use of either local guidelines (n=2) or referring to NICE ataxia guidelines (n=4). However, a larger proportion of respondents (n=36, 47%) reported they did base their intervention on research evidence. The comments suggested that respondents adapted guidance from relevant literature about other clinical populations to children with ataxia (e.g. strengthening in children with cerebral palsy) as well as using the Ataxia UK Best Clinical Practice guide (Ataxia UK 2016).

Table 6.9 – Use of clinical guidelines and research evidence (N=76)

	Number of respondents (%)
Base practice on clinical guidelines	
Yes	6 (8)
No	70 (92)
Base practice on research evidence	
Yes	36 (47)
No	38 (53)

6.14.3 Section 3 – Virtual Training

Fifty-seven percent of respondents (n=44) reported they had used virtual training in their overall practice and therefore were directed to further questions on their experience in this area. Physiotherapists indicated they had used virtual training most commonly in children with PFT, acquired brain injury and traumatic brain injury as illustrated in Table 6.10.

Table 6.10 – Patient populations physiotherapists have used virtual training with (n=44)

Population	Number of respondents (%)
Posterior fossa tumours	32 (73)
Acquired brain injury (excluding posterior fossa tumours)	28 (64)
Traumatic brain injury	27 (61)
Cerebral Palsy (CP)	10 (23)
Other (including 'hemiplegia', other oncology')	10 (23)
Developmental Delay	8 (18)

Benefits/challenges to using virtual training in children with posterior fossa tumours

Respondents gave details regarding their top three benefits and challenges to using virtual training in their practice with children with PFT. Twenty-five respondents answered this question, and all answers were considered.

Benefits to using virtual training revealed three broad categories of responses: engagement/compliance, physical benefits, and resource/equipment benefits.

Engagement/compliance was the most frequently raised benefit with physiotherapists repeatedly reporting that virtual training was "*fun and engaging",* and *"games are fun"*. This method of therapy was thought to be "*patient friendly"* and offered a way to achieve "*good compliance"* whilst being motivational. Physiotherapists noted the potential physical benefits from using virtual training including the ability to work on specific problems such as upper limb co-ordination and balance. Resource/equipment factors were also raised as a positive aspect with two respondents noting the potential for the technology to "*track progress"* and that the technology is easily available *"no additional equipment required"*, as children have "*access to [it] at home"*. Particular to the Kinect Xbox another respondent also

noted that they "*can see what [the] body is doing using Kinect*". Two responses that did not fall within these three broad groups related to involving the family in the therapy, with one of the physiotherapists noting it can be used as a "*family trainer"*.

Challenges to using virtual training can also be grouped into similar categories (engagement, physical and equipment/resources), although the responses given highlight problems in these areas to using this type of technology. Physiotherapists were concerned that children might become frustrated if they could not play a game they could before they had become ill, and one physiotherapist highlighted that virtual training might be "*demotivating if difficult"*. Physical barriers/challenges were noted with respondents raising concerns that if children had visual difficulties or significant mobility problems this might limit their potential to use this intervention, with one physiotherapist noting it could be "*difficult if child can't stand"*. The most frequent response regarding challenges to virtual training focused on equipment/resource issues. The responses centred on two areas, access to the resource or technical difficulties to using it in this specific population. A physiotherapist reported that it was "*not timely to set up"*, and another reported that "*it wasn't sensitive enough to use"*.

Twenty-five respondents answered the question regarding possible solutions to overcoming identified barriers, although only 11 of the 25 (44%) reported they had found potential solutions. These comments highlighted particular types of virtual training (GRAIL system and Tyromotion) that are not currently on the market in the UK. Strategies around game play were also raised with the need for physiotherapist supervision highlighted. The majority of therapists (n=23/30, 77%) who had used virtual training in their practice reported they encouraged families to continue to use this as part of their home exercise programme.

Reasons why therapists have not used virtual training in their practice

Thirty-two physiotherapists responded to the question on why they had not used virtual training in their practice. As this area was of particular interest to subsequent elements of

this thesis the responses were explored further. All answers were thematically analysed (Braun & Clarke 2006 a,b). The therapists who responded to these questions were from seven different countries, and 24 were working in an inpatient and six in an outpatient setting, and two were predominantly community based.

Two themes are presented from this analysis: resource issues, and condition specific clinical issues.

Resource issues

Resource issues were raised by a number of respondents with two main reasons highlighted; either relating directly to equipment itself or linked with related issues to staffing.

In terms of equipment, 18 physiotherapists reported they did not have access to virtual training equipment, and this was the most common response for this question overall. Further detail was provided by some physiotherapists to highlight that funding was the specific reason for lack of equipment, e.g., *"no funding available for applicable technology. Trust has been approached on several occasions. Tend to recommend generic options to families"*. The challenge of funding equipment when technology is constantly moving forward was also raised, as one respondent explained *"[I'd] like to use more but funding for equipment is often a block to more up to date hard/software".*

Even if the virtual training equipment was available there was also concern regarding the staffing implications of this intervention from two perspectives; time required to deliver the therapy (including set up time), and also the time required to train staff in this modality, e.g., *"staffing levels and caseload prohibit exploration of new innovative therapies"*. These responses reflect concern from physiotherapists that virtual training is possibly more complicated to deliver and has more training implications than other adjuncts to therapy. One respondent stated that *"honestly don't like to use computers; can't figure out how to use them (I'm old school and wasn't raised with video gaming--sorry!!!)"*. All the respondents who raised training needs as an issue were experienced physiotherapists (over 10 years

qualified), possibly highlighting additional perceived training needs, although there were also a number of therapists (over 10 years qualified) who had used virtual training and reported the positive aspects of this, indicating that level of experience does not necessarily need to be a barrier.

Condition specific clinical issues

The second theme identified related to clinical issues specific to children following surgical resection of a PFT. Two elements were raised; time pressures to discharge/transfer children as this impacted on time available to treat, and the appropriateness of this type of modality in the acute setting. Respondents noted that their treatment choice might be influenced by a short inpatient stay initially on the neurosurgical ward either due to required transfer to oncology for further treatment *"short stay on neurosurgical ward before transfer to oncology"* or transfer to facilities closer to home *"as a tertiary centre patients are quick to be discharged home or to local hospital"*. The potential for short inpatient stays and initial acutely changing presentation of the child were raised as factors influencing physiotherapy treatment choice with one respondent stating that virtual training was "*not felt most clinically relevant treatment method for [acute] stage of recovery".*

6.14.4 Section 4: Intensity and timing of treatment

The focus of the next section of the e-survey was intensity and timing of treatment. Physiotherapists reported they did intensify rehabilitation for children with PFT at certain time points (n=63, 86%), although the rationale for this varied. A common time point was immediately post operatively (n=31, 42%). A high number of respondents also selected the 'other' option (n=29, 40%). Subsequent detail given for this 'other' response demonstrated that physiotherapists tailored their intensity of treatment to the child's individual needs, which could be influenced by chemotherapy/radiotherapy the child might be receiving (Table 6.11).

Table 6.11 – Intensification of physiotherapy treatment (N=73)

	Number of respondents (%)
Intensify rehabilitation?	
Yes	63 (86)
No	10 (14)
If yes, when?	
Immediately post op	31 (42)
Following completion of all adjuvant treatment	8 (11)
No reason given	5 (7)
Other	29 (40)
'based on assessment of individual child at a given time',	
'aim to maintain during treatment, and then encourage local/community services to plan to complete a block of therapy post treatment to give them a boost and hopefully improve function'	
'we see the child after discharge from hosp & therapy is most intense from the start'	
'as indicated by child, may be post op, might be post chemo/RT'	

The most common intensity of treatment (n= 31, 42%) in the inpatient setting was four to five times a week, with a small number of physiotherapists (n=9, 13%) reporting treatment might occur more frequently than daily. There was a much more varied response from physiotherapists working in the community setting as highlighted in Table 6.12 and treatment was typically less intense than that provided in the inpatient setting. There was broad consensus on length of physiotherapy session with 89% (n=64) of respondents reporting sessions lasted between 30 minutes to an hour.

Table 6.12 – Intensity/length of physiotherapy Session (N=72)

Intensity – In patient setting	Number of respondents (%)
4-5 times a week	49 (68)
2-3 times a week	5 (7)
Once a week	0 (0)
Fortnightly	1 (1)
Monthly	0 (0)
Not applicable I don't work in the acute setting	8 (11)
Other (including 6-7 times a week, 8-10 times, sometimes twice daily, varies on child)	9 (13)
Intensity – Community/Outpatient setting	

4-5 times a week	1 (1)
2-3 times a week	9 (13)
Once a week	10 (14)
Fortnightly	3 (4)
Monthly	4 (5)
Block of therapy treatment followed by review	7 (9)
Not applicable I don't work in the outpatient/community setting	29 (41)
Other (depends where the child lives, initially more frequently then weans, varies on child)	9 (13)
Length of physiotherapy session	
<30 minutes	7 (10)
30-<45 minutes	39 (54)
45-<60 minutes	25 (35)
>60 minutes	1 (1)

Respondents were also asked how long (on average) their therapy intervention continued for children with posterior fossa tumours. Responses varied with a relatively even spread of answers from under three months to over two years. This variability reflects the differing needs of children with posterior fossa tumours where some children may have minimal deficits and require input only in the immediate post-operative period to a proportion of patients who continue to require input several years post-surgery. There was agreement that the majority of input is delivered on a one-to-one basis by a physiotherapist (n=52, 73%, see Table 6.13)

Table 6.13 – Duration and delivery method of physiotherapy (N=71)

Duration and delivery	Number of respondents (%)
Duration	
0-3 months	14 (20)
4-6 months	17 (24)
7-12 months	14 (20)
1-2 years	15 (21)
Over 2 years	11 (15)
Delivery	
1:1 by physiotherapist	52 (73)
1:1 by therapy assistant	0 (0)
Group setting	0 (0)
MDT therapy session	9 (13)
Home exercise programme	2 (3)
Other (e.g. combination of above, with joint sessions with OT/SALT)	8 (11)

Over one third (38% n=28) of respondents reported that therapy sessions were not optimally timed. Twenty-seven physiotherapists provided additional comments highlighting specific issues including availability of rehabilitation on discharge from the acute inpatient setting, impact of chemotherapy and radiotherapy (which may not be on the same site) which can mean the child may miss sessions due to being unwell, and problems with staffing/resources whilst there is an ongoing pressure from families for discharge home. The most frequent problem identified by twelve of the respondents was lack of community therapy input. Respondents also emphasized the importance of home exercise programmes. These topics were raised again when therapists were asked to highlight the challenges overall in treating children with posterior fossa tumours and are explored in more detail in the following section.

6.14.5 Section 5: Aims and outcomes

Physiotherapists reported common aims for treatment including improving co-ordination, balance, providing education to the child/family regarding activity and improving muscle strength. Aims highlighted in the 'other' comment option centred on improving function and return to participation for the child's individual goals. Reducing fatigue was also raised by one therapist (Figure 6.6).

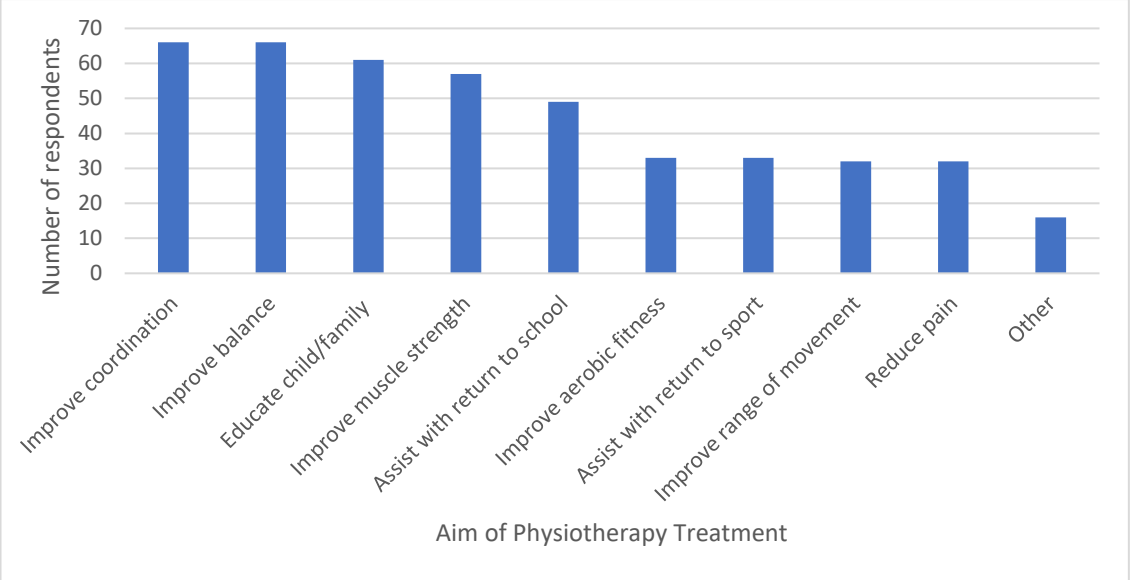


Figure 6.6 – Aim of physiotherapy treatment

Goal setting

Physiotherapists also highlighted they take several factors into account when goal setting with this group of patients. Sixty-nine respondents answered this question and all answers were reviewed to identify themes. The broad areas raised included child specific factors, family factors, and disease specific factors, whilst maintaining a focus on achieving function and participation targets.

Within child specific factors there were two main areas; consideration of the child's age, and issues relative to the child's specific impairment, e.g., "*fatigue*" and "*pain levels"*. Family factors were frequently mentioned by the respondents and predominantly centred around ensuring that therapy goals met the family's goals and expectations. Disease specific factors were also noted to impact on goal setting e.g. "*overall level of medical status*" and *"limitations of disease and treatment"*. Though despite these disease specific factors, physiotherapists tried to ensure that goals were achievable "*most important factor, realistic – patient able to achieve it*". Physiotherapists consistently noted functional and participation targets were considered during goal setting, with one respondent reporting that the importance that goals *"[are] relevant – will assist the patient in their day to day task"*.

Outcome measures

Seventy five percent (n=52) of physiotherapists reported they used standardized outcome measures to assess children with PFT. The most used outcome measure was the SARA (n=28). Other frequently used scales were the Berg/Paediatric Balance Scale (n=11) and the GMFM (Gross Motor Function Measure) (n=8) (Table 6.14).

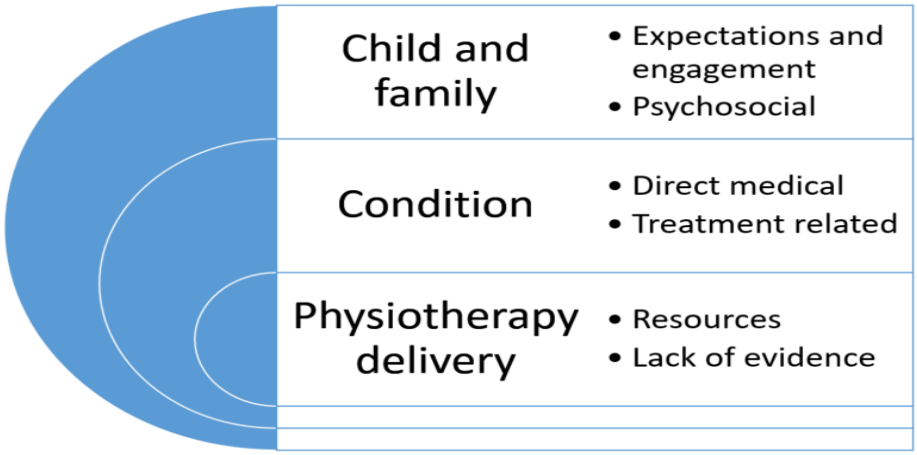
Table 6.14 – Standardized outcome measures Used (N=69)

Outcome Measure	Responses
SARA (Scale for the Assessment and Rating of Ataxia)	28
BBS (Berg Balance Scale)	11
PBS (Pediatric Balance Scale)	8
Gross Motor Function Measure (GMFM)	8
FIM/FAM (Functional Independence Measure/Functional Assessment Measure) or WeeFIM	6
6MWT (Six-minute walk test)	4
Time up and go	5
10MWT (Ten-minute walk test)	3
HiMAT (High Level Mobility Assessment Tool)	3
GAS (Goal Attainment Scaling)	3
PEDI (Pediatric Evaluation of Disability Index)	2
MAS (Modified Ashworth Scale)	2
Oxford (Muscle strength scale)	2
BOT(2) (Bruininks-Oseretsky Test of Motor Proficiency)	2
Bayley Scales of Infant and Toddler Development	2
Others with 1 response Rivermead Mobility Index, ICARS (International Cooperative Ataxia Rating Scale), Tinetti Test, MFT (Manual Function Test), Mvt ABC (Movement Assessment Battery for Children), RCS (Rehabilitation Complexity Scale), GOS (Glasgow Outcome Scale), AIMS (Alberta Infant Motor Scale), ROM (Range of Movement), CAPE (Children's Assessment of Participation and Enjoyment), Peabody Developmental Motor Scales, St Judes Questionnaire	1 each

Reported problems/challenges

Sixty-nine respondents from UK, Europe, USA/Canada, and Australia/New Zealand reported the frequent problems/challenges they encountered when treating children following surgical resection of PFT and all answers were thematically analysed. The respondents had a range of experience in working with children with posterior fossa

tumours, with the majority of therapists having worked in this field for over 5 years as reflective of the overall sample who entered the e-survey. Three main themes were identified, each with two subthemes (Figure 6.7).



Child and Figure 6.7 – Thematic map; problems/challenges encountered when treating children following management of a posterior fossa tumour

Family factors

Physiotherapists repeatedly raised challenges to rehabilitation in terms of child and family factors both from an emotional/psychosocial perspective and expectations/engagement (child and parents). The respondents' views on this area demonstrate how emotive treating a child with cancer may be, and that these issues can have a significant impact on progress of the child's rehabilitation. This topic was the area on which physiotherapists provided the most extensive accounts, highlighting how much this element can influence their practice. Emotional and psychosocial factors arising from the impact of the illness on the child were reported as challenges by the respondents such as the *"loss of friendship groups and social life"*. Respondents believed the recovery period could be an isolating time for the child and their family. Even when treatment has finished respondents suggested that children may not be at a physical/cognitive level which enables them to return to their previous activities, and one respondent stated, *"psychosocial issues around functional loss had huge impact on participation".* Another respondent noted that *"changes in child's personality, cognition,*

speech, physical abilities & the effect on child, family & their friendships etc." were all challenging. However, even if the respondents are aware of the potential psychosocial factors and emotional stresses, they reported it can still be difficult to manage the child and family's expectations of rehabilitation. The challenge of engaging families in the early stages post operatively when the child may be viewed as acutely unwell was emphasized by physiotherapists, and typified by this response *"initially post op barriers are gen [generally] related to family and their views on Sx [surgery] – families very over protective with the patients – tend to be slow to get up and move"*. Additionally, following on from the acute neurosurgical phase there is then the challenge of continuing to integrate rehabilitation during the child's oncology treatment when again they might be unwell, with one respondent noting the challenge of *"parental coping and mental space to think about rehab versus oncology treatment"*. This view was supported by another respondent who noted the *"priority of chemotherapy/radiation vs physical therapy".* Respondents noted it was crucial for the family to engage in the rehabilitation process through *"family buy in"* to enable ongoing practice of activities/working towards shared goals but reported that parents commonly regarded rehabilitation as a low priority until after oncological treatment had finished as *"sometimes the parents don't want the therapists to work with their kids if they are hurting".* Engagement directly with the child was also seen as important to maximize therapy sessions, although this challenge was not raised as frequently as the challenge of working with the families. Physiotherapists noted that some children had difficulty engaging with older staff as they were *"too much like mum, just nagging*", highlighting the importance of rapport-building between the child and the physiotherapist.

Condition specific factors

Direct medical problems included the impact of the tumour itself and the potential of new neurological deficits following neurosurgical intervention (e.g. cerebellar mutism syndrome). The impact of subsequent oncology treatment was also raised by the majority of respondents (n=24). Side effects of chemotherapy/radiotherapy were noted which impact

upon the child's ability to participate in rehabilitation, e.g., *"fatigue due to adjuvant treatment"*. A number of respondents (n=9) commented that fatigue can be exacerbated by the child having to travel to another hospital site for radiotherapy; one respondent noted that *"during RT patients have to travel, difficulty planning rehab"* and another noted that *"children transfer to a different hospital for chemo/radio so disjointed service"*. Mobility specific side effects such as chemotherapy induced peripheral neuropathy or steroid related myopathy were also reported *"loss of joint range following certain chemotherapy treatments"*. These issues mean rehabilitation can be even more important to assist with the child's return to function and participation, but they also directly impact on the delivery of therapy interventions.

Physiotherapy delivery factors

The challenge most frequently highlighted by the physiotherapists related to actual delivery of therapy input. This is presented in two areas: resource factors and lack of evidence. In terms of resource deficits, the area highlighted was physiotherapy staffing levels with respondents commenting that *"staffing [problem] as often need intensive physiotherapy post-surgery and discharged home"*. This seemed to be particularly influenced by a perception of pressure to discharge the children home quickly, e.g., *"caseload on a neurosurgical ward-time until discharge to home"*, alongside problems with subsequent community/local physiotherapy input on discharge home. One respondent described the challenge as being *"DGH only with limited therapy; community has variable expertise and staffing"*. The impact of the child receiving input between two sites e.g., neurosurgical and oncology, also raised challenges from a staffing and resource perspective, e.g., *"Multi centre, so surgery not performed at oncology hospital and much of it is also community based which is not provided by oncology hospital due to geographical limitations"*. In addition to staffing requirements, challenges related to space and equipment were also raised, including *"limited space and equipment"* and *"no dedicated rehab team/ward"*. The frequency of responses in terms of staffing and resources indicated that physiotherapists

report this as a major challenge in providing input to this population. However, staffing was not raised as an issue by physiotherapists in the USA/Canada (although lack of insurance was noted later in the survey in challenges to transition) highlighting how differences in provision of healthcare across different countries may influence the challenges to physiotherapy intervention.

In addition to resource issues, the other area that respondents felt directly impacted on physiotherapy input is the lack of evidence for therapy input in this area. This was detailed repeatedly by physiotherapists who noted the *"lack of research"* and *"limited evidence especially clinical guidelines"*. This was followed by the recognition that lack of evidence in this area can directly impact on the ability to bid for additional staffing as the evidence in this area is not available to support such business cases, despite rehabilitation being expected by the wider MDT and families. It was noted that there is *"minimal evidence on optimum treatment and therapy input to fund longer sessions...of treatment".*

The challenges raised by the therapists indicate the complexity of providing rehabilitation for children with ataxia following surgical resection of PFT, with condition specific factors unique to this population influencing subsequent child and family factors and balancing this alongside ongoing staffing and resource issues.

Transition

Respondents were also asked about problems they have identified in relation to transition of care at different time points ranging from discharge home from the acute hospital, transition/reintegration back into school or transition from child to adult services. The question regarding transition to adult services was answered by the lowest number of physiotherapists (41 respondents from across UK, Europe, USA, and Australia/New Zealand), with some physiotherapists reporting it was not applicable to their area of practice. Overall, a diverse range of issues were described by the respondents. No strong themes emerged due to the variety of challenges reported. However, broad areas summarised as

resource issues (both therapy provision and school support), communication, physical difficulties and families' expectations are reported below.

Problems identified from inpatient to outpatient setting centred on the availability of ongoing rehabilitation in the community/outpatient setting. Respondents described issues such as *"staffing and available settings for treatment not possible in patient's home (use of equipment etc"), "difficulty attending local services, due to frequent hospital admissions",* and *"poor tertiary outreach"*. Communication was also raised as a potential problem highlighting the number of professionals that might be involved in the child's journey and the need for ongoing discussion between professionals. Respondents shared problematic cases such as *"very poor communication between hosp [hospital] & community"* and *"transition not well planned at all, lack of communication/discharge plans".* Another physiotherapist explained that "*changes in people and teams often difficult for patients"*. The issue of lack of insurance was also raised which obviously is a consideration in some countries.

In terms of transition back into school, resource issues were noted in relation to *"equipment provision within the school".* However, the child's physical status was also seen as a challenge especially in terms of fatigue and their ability to tolerate the school day, e.g. "*fatigue fitting in school and physio"*. Resources were again raised when considering transition into adult services. A lack of appropriate rehabilitation centred on young people's needs was also expressed by respondents; one respondent noted that with "*16-17-year olds not always clear whether paediatric or adult services, Get treated like a 60 year old stroke patient + discharged when not reached full potential"*. Also, at this time point "*managing expectations of families"* was a concern, with one physiotherapist suggesting the need for earlier preparation/advice on managing the young person's needs more independently prior to the time of transition, with the young person "*learning to take more responsibility for progress"*. Another physiotherapist reported *"patients do better if they are assertive/advocate for themselves".*

The final question of the survey asked physiotherapists to document their main reasons for discharging a child who presented with ataxia following surgical resection of a PFT. The most common answers were whether the child's goals had been met (n=50, 71%), or if there was a plateau in physical function (n=43, 61%). Other responses highlighted by the respondents included time of transition, e.g. discharge from acute care to community services closer to the child's home or to palliative care teams. Family disengagement was also reported as a potential reason for discharge. The range of responses is illustrated in Figure 6.8.

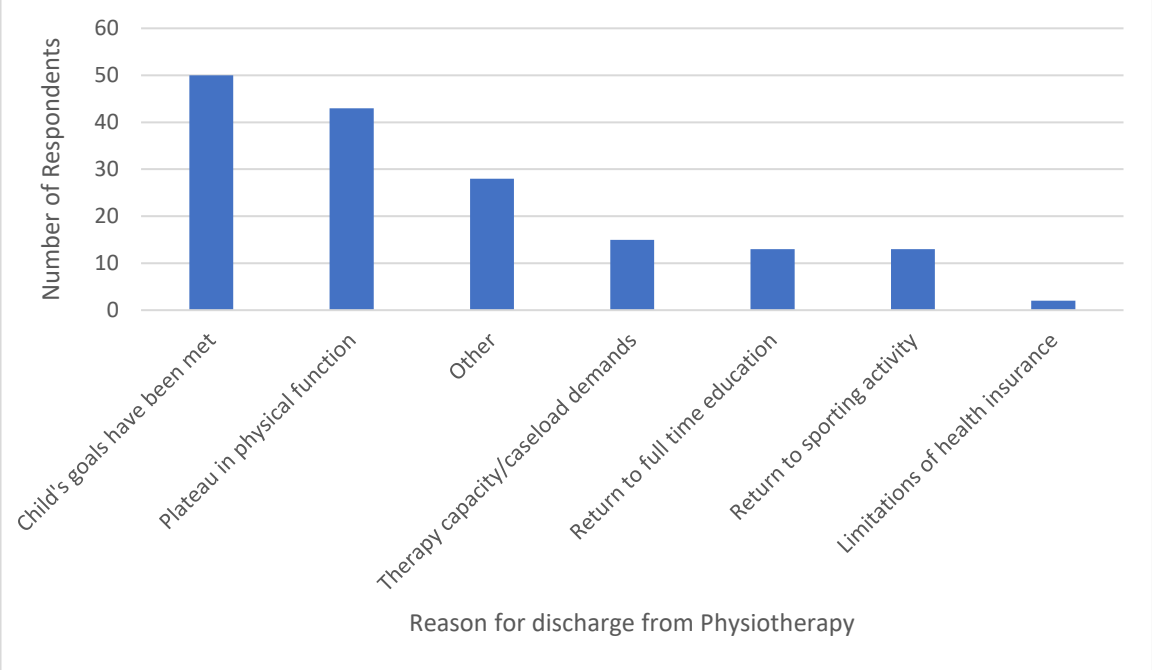


Figure 6.8 – Most common reason for discharge from physiotherapy

6.15 Discussion

This study provides a unique contribution to the understanding of current international practice for children with ataxia following surgical resection of PFT, providing new data that have not previously been reported. Overall the objectives of the e-survey were to: gain an increased understanding of current physiotherapy practice in relation to the treatment methods used; understand the challenges to physiotherapy management in children with

PFT; explore physiotherapists' views of the use of virtual training in this population group; generate an understanding of the range of the intensity and timing of treatment; and inform the subsequent phases, in particular the rationale underpinning the feasibility RCT. Information has been gathered to satisfy each of these accordingly, and the results and subsequent implications of each section of the e-survey will now be synthesised and presented.

6.15.1 Synthesis of results

Respondent characteristics

Over 90 physiotherapists from across 12 countries completed the e-survey exceeding the targeted aim for number of responses. Although the largest cohort was from the UK there was good representation internationally, particularly across Europe. The response rate is not known due to the request to snowball the survey. Completion rate for the e-survey was 41%, this was known to be affected by the individual applicability of some questions e.g. if a physiotherapist had not worked in a particular setting as the focus of a question, it would not be applicable to answer.

The majority of respondents had been qualified for more than ten years, which suggests that they had a broad range of experience to draw on when answering questions. However, these experienced physiotherapists also reported looking for but failing to find post-graduate training opportunities in this field, highlighting a potential gap in this area. These findings indicate that physiotherapists may lack opportunities to develop specialist knowledge. NICE Neuro-oncology Guidelines (2005) recommend that clinicians involved in this specialist area should have access to training although there was no further literature sourced that identified a lack of availability of specialist training in this area for physiotherapists. Formal post graduate training e.g. such as an MSc Neuro Rehabilitation offers scope for individual physiotherapists to develop their own interests but there is no formal clinical (or academic) training in this area has been identified. There is a development framework with allied health

professionals working in the wider context of adult oncology (Macmillan Oncology competencies) but no paediatric equivalent.

Physiotherapists who answered the survey worked across a variety of settings though predominantly in the inpatient setting. This is consistent with these physiotherapists having the highest caseload in this area, with children initially managed in specialist centres in an inpatient setting, then care may be gradually transferred out to the community setting. This is in keeping with recommended specialisation of care for children with brain tumours (NHS Specialised Commissioning 2009).

Therapy interventions

Balance exercises, gait re-education, proximal control exercises and task specific training were the most commonly used interventions reported by respondents. Balance exercises are regularly used in neurorehabilitation, and there is some evidence of effect for adults with ataxia (Fonteyn et al. 2014, Marquer et al. 2014), though a lack of evidence specific to paediatric PFT is noted. The use of proximal control was also widely supported, especially in the UK. Although commonly used as a treatment for ataxia, research evidence to support its efficacy is lacking. It was noted that there were slight differences between UK and European practice. Interventions such as neurodevelopmental therapy (NDT), a rehabilitation method based on a hierarchical central nervous system with an emphasis on individualised therapeutic handling (www.ndta.org), and Votja therapy (therapy derived from the former Czechoslovakia based on reflex locomotion www.votja.com) were used more commonly by respondents from the rest of Europe rather than in the UK. This is in keeping with the literature examining the effectiveness of NDT and Votja approaches which report they are more commonly used to date in Europe (but outside of the UK) (Jung et al. 2017). Though in the literature review there was no supporting evidence found for the specific use of NDT and Votja approaches in children with ataxia (apart from the single article by Knox et al. (2002) that included 2 children with ataxia but their data were unable to be extracted). Despite the differences in the use of NDT and Votja approaches between respondents in

the UK and those in the rest of Europe, the four most commonly used interventions were the same across all the geographical regions. These findings suggest that there was a degree of consensus about the most commonly used interventions.

Adjuncts to treatment reflected consistent practice across different countries/level of experience, with orthotics and mobility aids reported to be the most commonly used and deemed the most effective by physiotherapists. This is despite there being no specific evidence published on the effectiveness of mobility aids/orthotics in children with PFT. Further exploration of the type of orthotics used and the aim of this intervention adjunct may be useful in future research to understand the high frequency of their use. There was also support for treadmill training, weighted therapy, taping/lycra garments and virtual training to be used as part of a treatment programme. Low level evidence (OCEBM level 3 and 4) supports the use of treadmill training (OCEBM level 4) and virtual training in children with genetic ataxias (Ilg et al. 2012, Schatton et al. 2017 (OCEBM level 3)) as discussed in Chapter 3 and in Hartley et al. 2019). There is less certainty regarding the benefit of weighted therapy and taping/lycra garments (Fonteyn et al. 2014). The single paper reported in the literature review utilising lycra garments observed mixed results in the one child with ataxia from their sample (Nicholson 2001).

Clinical guidelines/teamworking

Just under half of the physiotherapists reported that they based their intervention on research evidence, typically citing relevant literature on the management of ataxia (the most commonly mentioned document was the Ataxia UK Clinical Guidelines 2016), the physiotherapists themselves acknowledging the lack of specific literature in this field. Although physiotherapists did report referring to the NICE Ataxia Guidelines, there are no specific NICE guidelines; however, an internet search for NICE ataxia guidelines does direct the search to the Ataxia UK Clinical Guidelines, so this may have been what the respondents were referring to. Very few (n=6, 8%) physiotherapists reported using any

local/national clinical guidelines in this area; this finding probably reflects the lack of clinical practice guidelines in this field. The development of clinical guidelines could help to identify best practice for the child and their family through the rehabilitation process post-surgery and may also facilitate consistency of service delivery (Grol & Grimshaw 2003). Two thirds of the therapists reported they did work as part of a specialist Neuro Oncology Rehabilitation Team.

Team-working is recognized as important in rehabilitation to enable a cohesive approach with children who typically have a number of professionals involved in their care (NICE 2014). There is also emerging literature supporting a multidisciplinary team approach as best practice in the rehabilitation of both adults and children with brain tumours (Vargo et al. 2016, Fountain & Burke 2017, Adcock & Burke 2014). A team approach may be particularly important in this population group where due to the long term follow up required there may be a number of transition points in their care e.g. such as from neurosurgery to oncology, then into community management, and ultimately, into late effects follow up; thus communication between professionals is essential (Vargo 2011). The presence of such specialist teams provides the basis of expertise which could help in the formulation of national clinical guidelines such as seen recently in the development of the Stroke in Childhood Clinical Guidelines (RCPCH 2017). However, developing evidence based clinical guidelines for ataxia in childhood would be challenging in view of the lack of evidence in this area. This raises the need for quality research in this area to provide evidence to guide the development of clinical guidelines to attempt to improve patient outcomes by reducing inconsistencies and ensuring patients access the most beneficial forms of treatment (Chassin 1990, Grol and Grimshaw 2003). Indeed, the Paediatric Neurosciences Physiotherapy Network (comprising of the Acquired Brain Injury and Oncology Paediatric Physiotherapy Networks) identified the creation of a neuro-oncology patient pathway as a priority for the upcoming network objectives (Joint Paediatric Neurosciences/Oncology Meeting 2018).

Virtual Training

A number of physiotherapists had used virtual training in some format in their practice, most commonly with children with PFT. This result suggested that the proposed intervention for Phase 4 of the study would be focused on an area of interest and practice relevant to clinicians. Virtual training in this instance was defined as the use of computer technologies that provide an interactive environment that requires limb movement to react to on screen game play (Vernadakis et al. 2014). Although the use of off-the-shelf versus bespoke technology was not explored this may be of value to consider in the future. The results are also in keeping with the literature review which demonstrated a trend towards effectiveness when utilizing technology for therapy management of children with ataxia (Ilg et al. 2012, Synofzik et al. 2013, Sabel et al. 2016). Physiotherapists identified a number of benefits to using virtual training both in terms of engagement for the children which was repeatedly mentioned (and is reported in the literature Bonnechere et al. 2017, Meldrum et al. 2012) and potential clinical gains such as working on co-ordination. The potential impact on co-ordination is also supported by literature (Wuang et al. 2011) although the majority of the literature is focused on balance in particular (Sharan et al. 2012, Ilg et al. 2012, Jelsma et al. 2012) which was mentioned by the respondents but to a slightly lesser extent. The ability to record progress was also seen as a benefit by the physiotherapists along with the potential for family members to participate in the training programme and continue with this at home although these aspects have not been explored in the literature on virtual training. Challenges raised to using virtual training included access to equipment and training requirements, and specific issues of the gaming systems used such as them not being sensitive enough; similar benefits and challenges are reported in Levac et al. (2012) and Levac and Miller's (2013) exploration with clinician's experiences of virtual reality working with children with acquired brain injury. Additionally, physiotherapists in this e-survey noted that a possible challenge to the use of virtual training was frustration experienced by the children especially if they could not do an activity they could do before. Although a sense of frustration could apply to a number of functional based therapy interventions, this should be

considered when planning an intervention. Interestingly physiotherapists did not highlight uncertainty regarding effectiveness of the intervention as a challenge to its use, instead focusing on practical implementation issues. Resource and condition specific issues were identified as reasons why some physiotherapists had not used virtual training in their practice. These factors could also be considered as interlinked as a short neurosurgical inpatient stay is often encouraged either to allow discharge home or quick transfer to start oncology treatment (which is unique to this population). Therefore, the focus may be on very specific functional tasks at this time e.g. gait re-education/activities of daily living to facilitate discharge or transfer, instead of alternative methods of virtual training. It might therefore be useful to explore further at what stage post operatively physiotherapists have successfully used virtual training to see if these perceived barriers could be changed.

Intensity of intervention

Intense treatment being offered in the in-patient setting was noted as common practice, followed by grading of input after discharge/transition to community settings. There is no specific literature published to date in this population to support this choice and this potentially could be influenced by workforce infrastructure. However, the reduction of input after the acute in-patient stage may link in with the findings of Phase 1 of the study where it was observed that there is a rapid change (drop) in ataxia severity in the first three months post-surgery and then gradual change up to three years post operatively. This is also supported with the literature on rehabilitation of adults with brain tumours reporting significant functional gains in the acute rehabilitation process, with the most gain found during the initial inpatient stay (Marciniak et al. 2001, Vargo 2011). Improvement in the initial rehabilitation stage has also been demonstrated in children with brain tumours (not specific to PFT) (Bedell 2008). However, interestingly improvement in health-related quality of life but not physical activity gains have also been reported in children with brain tumours (mixed location) and bone tumours after a four week inpatient rehabilitation stay on average 17 months post treatment (Muller et al. 2016). Physiotherapists reported they commonly

intensified therapy treatment at certain time points, with immediately post operatively the most frequent time which is reflected with increased input in the inpatient setting. However, also they identified a strong trend of individualizing intensity of therapy input taking several factors into account such as adjuvant treatment, fatigue, and availability of ongoing community services. An individualised approach is recommended in paediatric neuro-rehabilitation for other conditions e.g. such as childhood stroke (RCPCH 2017).

It was interesting that there was broad consensus of physiotherapists with regard to intensity and length of physiotherapy sessions even though the small body of literature in this area reports a wide range of therapy dose (duration of intervention 2 to 19 months, intensity 10 minutes to 60 minutes per session, frequency once every 3 months to six days a week (Hartley et al. 2019)), and thus makes it difficult to draw comparisons across studies. The intensity of treatment (60 minutes per session, three times a week for 4 weeks, followed by home training) used in Phase 4 of this programme of work appears reasonable considering the intensity reported by physiotherapists in current practice. The majority of input was delivered on a 1:1 basis by a physiotherapist indicating how therapist dependent treatment is, especially as physiotherapy intervention may carry on for months and even years post initial surgical management (Hartley et al. 2018). This led to physiotherapists identifying that therapy provision is not always optimally timed particularly when the children may be having ongoing oncology treatment, although there is a lack of literature in this area to support this or to confirm the reasons why. These elements do highlight that effective therapy provision that could be carried out at home which is not 1:1 therapy based could be integral to optimizing a child's rehabilitation potential. There is literature in the cerebral palsy field that highlights the benefits of home exercise programmes for balance problems (Katz-Leurer et al. 2009) which could be built on with this population group.

Aims/individualised approach

The aims of physiotherapy intervention covered the whole World Health Organisation (WHO 2001) ICF framework, from those focusing on impairment (e.g. improving balance) to influencing activity (improving fitness) and also considering participation (e.g. assisting with return to sport). Respondents reported an individualised goal setting approach considering environmental and family factors alongside condition specific issues. Although there is no specific literature in the PFT population to support this, the use of individualised goal setting is evident in the wider literature on paediatric rehabilitation and in particular for children with cerebral palsy where there is a larger evidence base (McDougall & Wright 2009, Cusick et al. 2006).

Outcome Measures

Three quarters of therapists reported using standardized outcome measures, again highlighting areas of good practice, although the consistent use of standardized outcome measures is not reported in the literature in this area. It is only in more recent multinational neuro-oncology trials that motor outcomes are also being formally measured (e.g. use of the Brief Ataxia Rating Scale (BARS) in PNET 5, a multicentre international trial exploring outcomes for children with medulloblastoma, a malignant PFT). Survey respondents most commonly used the Scale for the Assessment and Rating of Ataxia SARA, which adds weight to the need to validate this measure in this population group as it is a tool used in practice and the most familiar to clinicians. The SARA is predominantly an impairment-based outcome measure and activity/participation-based outcome measures e.g. such as the PEDI were less widely used.

Challenges to therapy

It is broadly recognized that children with brain tumours can present with multiple needs and complex problems (NICE 2014, Bull et al. 2007), though this is the first time that physiotherapists' views across different countries have been explored identifying specific challenges to rehabilitation. Three themes emerged: condition specific factors, child and family factors and physiotherapy delivery factors. It is interesting that some of these

elements are beginning to recur as they were also described in relation to use of virtual training and transition, therefore these aspects are important to consider in the design of subsequent clinical trials. Although physiotherapy delivery factors such as resource issues are also reported in physiotherapy input for children with cerebral palsy (Taflampas et al. 2018), children with PFT present with unique challenges. These challenges relate to the potential for prolonged treatment, possibility of recurrence and potential life shortening disease. Physiotherapists frequently raised challenges related to parents' engagement and/or expectations, particularly relating to balancing rehabilitation post-surgery or times when the child might be unwell during radiotherapy/chemotherapy. Jones (2012) described the emotional reactions the child and their family may experience during the initial period post diagnosis, reporting shock, confusion and uncertainty about prognosis, treatment, and outcomes. The lack of time for children and families to react to their diagnosis and consider treatment options has also been reported (Ajovalasit et al. 2009), reflecting the adjustment families have to make to a wealth of news and information about a potentially life limiting condition for their child whilst physiotherapists are trying to encourage their child's participation in rehabilitation. Walker et al. (2014) reported two case studies of children who required rehabilitation for cerebellar mutism post-surgical resection of PFT. It was found that management in the early stages was reliant upon multidisciplinary therapy input. Further insights into the families' experiences during this timeframe were revealed and these included feelings of helplessness, loss of control and frustration due to lack of information. There is a lack of literature regarding parental expectations of rehabilitation in children with PFT. Recent work in this area with children with long term conditions such as cerebral palsy focuses on the importance of taking the views of parents into account when planning rehabilitation programmes (Kavlak et al. 2014). Understanding parents' perceptions of physiotherapy in this specific population is a potential area for future research.

Transition

Lack of community input and the challenges of fitting in rehabilitation around adjuvant oncology treatment were raised by physiotherapists, along with the importance of families/the child taking on more independence/responsibility for driving their rehabilitation programme. Physiotherapists noted problems engaging education staff in reintegration/promoting therapy goals in schools, and there were also concerns regarding teenagers having access to appropriate rehabilitation. In particular it was felt that adult services could not adapt to provide appropriate input to adolescents with acute neuro-rehabilitation needs. Similar issues regarding transition are also reported in the literature on children with complex neuro disability e.g. children with cerebral palsy (Chamberlain & Kent 2005). Although there is generally a lack of literature specific to teenagers with PFT on transition, there is a single report by Biassoni et al. (2017), looking at children who had survived a brain tumour, that observed similar issues to those reported in the e-survey with regard to school re-integration (i.e. environmental issues). They also highlight that a combination of physical, psychological, and social factors (both from child and parent perspective) can impact on school reintegration.

Problems with fatigue were repeatedly raised as a factor affecting both rehabilitation and subsequent reintegration into an education setting. This has been increasingly raised in the literature (Chang et al. 2013, Davies et al. 2002, Hockenberry-Eaton & Hinds 2000), therefore, potential for fatigue should be considered when planning rehabilitation intervention/clinical trials particularly if they are occurring at a time the child might also be increasing their time in education.

6.15.2 Limitations

The e-survey was purposefully designed because a questionnaire that measured the constructs of interest had not been previously published. The e-survey was therefore tailored to the specific objectives of the study, but the fact that the tool was not validated is a limitation. Additionally, the internal consistency of the survey was not tested. This could

add value if the tool was adapted for use in the future to ensure that constructs such as treatment interventions were adequately covered (with agreement demonstrated between items). Although a relatively large sample was obtained, it is acknowledged there was scope to gain further views from physiotherapists across the USA and other countries to gain additional knowledge from physiotherapists who might have significant experience in this area. A larger international representation would have been useful to ensure the results reflected practice across different countries and may have also highlighted differences across health systems. It is also noted that many countries, e.g., those in Asia, Africa and South America were not targeted due to links to relevant networks not being available. Additionally, the potential response of the e-survey internationally was limited as it was only available in English (due to time and financial constraints). Snowballing the survey and sending it out through gate keepers to special interest groups did facilitate a response from nearly 100 physiotherapists although this method does mean it is not possible to calculate the response rate. However, the target number and subsequent number of responses in this survey could inform sample size estimations in future similar studies.

It is acknowledged that targeting special interest groups might raise a potential bias as members of an interest group are potentially more likely to be following best practice which could be less representative of the whole professional group. However, in order to gain views from physiotherapists who were experienced in the field this was considered the most appropriate source for the sample population. The survey was anonymized to allow open responses but a limitation of not capturing IP addresses is that if network connectivity is lost the responses stop under this IP log in. If this occurs, the respondent has to re-enter the survey to gain a complete response, but in this instance, they are counted as a new respondent. Completion rate of all questions for the survey (of surveys started) was 41%, this was influenced by the fact that some questions were not applicable for all physiotherapists to answer e.g., if they had not worked in that setting. However, it was noted there was a slight tail off in responses towards the end of the survey which could reflect

response fatigue due to the length of the survey. A shorter survey with fewer open questions may have achieved a higher completion rate. However, as this e-survey was an opportunity to gather as much useful information as possible this was balanced against time demands; the balance may not have been perfect.

6.15.3 Impact on Phase 3 and Phase 4

The e-survey provided useful information to inform the research in Phases 3 and 4. The need for such research was clearly indicated by the physiotherapists who frequently raised the issue of a lack of evidence and clinical guidelines, which suggested the proposed intervention study was focused on an area of interest and practice relevant to clinicians. The challenges raised regarding using virtual training were then explored in Phase 3 to maximize adherence in the subsequent trial. Enabling children to be involved in game choice assisted with sourcing games for the trial that had therapeutic value but also offered enough variability in game play to allow them to be engaging and challenging but not so inflexible that they would become frustrating. The information provided about the typical dose of physiotherapy interventions (frequency, duration and intensity) was used to inform the intervention study (Phase 4). The difficulties in terms of engagement in rehabilitation whilst undergoing adjuvant oncology treatment consolidated the decision for the inclusion criteria for Phase 4 i.e., 12 months post-surgical resection to allow treatment to be completed and for the family, potentially, to change their focus onto rehabilitation. Additionally, the information collected on use of outcome measures guided the selection of outcome measures for Phase 4.

6.16 Dissemination of findings

The e-survey was summarized for submission to ISPNO 2018 (International Symposium on Paediatric Neuro Oncology) as a poster presentation to facilitate discussion initially amongst health care professionals in the field of neuro oncology. A summary of results was also sent out via the networks to provide feedback to the respondents. This was also sent individually

to physiotherapists who specifically requested further information about the e-survey. The study was also submitted for publication to an international peer reviewed journal with a physiotherapy readership, and subsequently published (Hartley et al. 2020, Appendix 12).

6.17 Conclusion

This e-survey generated three key original findings; knowledge of the variety of treatment interventions (whilst highlighting the scope of virtual training), consensus of treatment intensity, and recognition by clinicians of the lack of clinical guidelines in this area. The e-survey also makes an important contribution to understanding the challenges to rehabilitation in this population group, whilst establishing the need for future research in this area.

Initially, in terms of treatment type, the e-survey demonstrates the wide range of intervention types used by physiotherapists with common adjuncts to treatment of orthotics and walking aids. Despite the lack of robust research evidence this e-survey also shows that virtual reality training programmes are used in contemporary practice for children with ataxia. This finding strengthens the need to carry out research in this area. Broad consensus was noted in terms of treatment intensity in the in-patient setting and regarding length of physiotherapy sessions.

The e-survey also demonstrated areas of good practice including multi-disciplinary team rehabilitation provision within specialised neuro oncology rehabilitation teams. Use of standardized outcome measures and an individualized approach to treatment planning and goal setting covering all domains of the ICF framework was also reported. Despite areas of good practice, physiotherapists were concerned about the lack of evidence to guide their interventions for children with ataxia.

The results also provide valuable information about the challenges to rehabilitation for this patient group, e.g., limited resources, condition specific clinical factors, difficulty engaging children and parents with physiotherapy interventions, and transition from acute to community rehabilitation. The identification of these challenges to current practice provides a base to consider the direction of future research that could lead to implementation of effective rehabilitation in the future. The findings suggest that engaging and time efficient interventions which target balance problems may be valuable, particularly if they can be used in both the home and clinical setting. The findings clearly raise the need for further research in this field to help with the development of physiotherapy guidelines in children with posterior fossa tumours.

Chapter 7 – Phase 3 – Workshops - Exploration of innovative technologies for use as virtual training intervention

7.1 Introduction

The trend for using virtual reality technology (VRT) as a physiotherapy intervention for children with ataxia was discussed in Chapter 3 in the literature review. The e-survey responses evaluated in Chapter 6 also confirmed the use of VRT in children with PFT in clinical practice, albeit with limitations. The combination of emerging use of VRT in the literature (Chapter 3), in clinical practice (Chapter 6), along with support from children as part of the patient and public involvement (PPI) group for its use as part of a research study, led to VRT being proposed as the intervention for Phase 4 of the study.

The first part of this chapter will summarise the literature on VRT in paediatric neuro-rehabilitation and also debate the theoretical foundations for VRT, with specific reference to cerebellar impairment. The use of the Xbox Kinect, in particular, will be discussed as a type of VRT that could be used in children with PFT.

The chapter will then move onto presenting workshops that were undertaken as Phase 3 of this study. These were conducted to provide an understanding of which type of VRT and which specific games might be appropriate for children with PFT to inform Phase 4 of this study.

To gain insights into which type of VRT offers both therapeutic value and is engaging for children, two workshops were conducted involving children, their parents, physiotherapists and gaming experts. Workshops offer a forum to facilitate discussion in small groups and allow practical engagement with the chosen topic, in this case enabling physiotherapists and children and their families to try different games and to gather feedback about the

strengths and limitations of each game and gaming platform. The work undertaken within these workshops is presented in the second part of this chapter.

Chapter 7 Part One; Use of VRT in paediatric neuro-rehabilitation

7.1.1 Use of virtual training in paediatric neuro-rehabilitation

VRT refers to the use of computer technologies that provide an interactive environment requiring limb movement to react to on screen game play (Vernadakis et al. 2014). VRT can also be referred to as active video gaming (Hickman et al. 2017) or exergaming/serious games (Synofzik & Ilg 2014). VRT throughout this chapter refers to non-immersive virtual reality training.

In addition to the evidence for exercise and physiotherapy interventions presented in Chapter 3 in children with ataxia specifically, virtual reality training has also been used in paediatric neuro-rehabilitation in children with other pathologies. Systematic reviews (n=13) published since 2009 (to 2019) have reviewed the effectiveness of VRT on a range of motor and functional outcomes in children with neurological pathology, developmental delay, or other movement impairment. The bulk of the literature is in children with cerebral palsy, though there are smaller individual studies that have also suggested VRT may of benefit in children with acquired brain injury. There are no studies specifically with children with PFT[3].

Due to word limitations within this chapter, the evidence, outcomes and recommendations from the 13 systematic reviews for children with other neurological pathologies (and individual trials for ABI) are presented in detail in Appendix 13.

Overall the evidence suggests that VRT is a feasible intervention for children aged 4-18 years of age with a range of health conditions and could be considered as a promising tool

[3] Literature published 2020 onwards is examined in the discussion (Chapter 9)

for improving outcomes in this population. However, further high-quality studies are needed to determine its value in children with PFT.

7.1.2 Theoretical foundations for virtual reality training

VRT systems have a number of attributes namely, the incorporation of repetitive task practice, the ability to target the whole body or isolated upper/lower limb movements, the use of fine motor control to interact in a visual environment and the requirement of maintaining an upright body position (Levac et al. 2016). It presents simulation of a real-world environment with engaging tasks and experiences designed to increase attention (Kitago & Krakauer 2013). VRT alongside physiotherapy input can control task timing, environmental stimuli and the use of augmented feedback to increase motor learning dependent on the choice of VRT system, gaming and physiotherapist instructions and feedback (Deutsch & Westcott McCoy 2017). The literature review (Chapter 3) demonstrated that VRT is part of contemporary practice for children with ataxia though there is clearly less literature in this field (compared to children with other neurological pathologies such as cerebral palsy) and the impact on motor learning on children with cerebellar pathology is less clear. The next section will consider the different concepts of VRT principles linked with motor learning, game design, and motor learning with specific reference to children with cerebellar damage.

Virtual reality training and motor learning

The overall aim of physiotherapy intervention is to drive neuroplastic central nervous system (CNS) changes and improve functional ability. VRT offers the potential to promote learning and possibly neuroplasticity (Cheung et al. 2014). Motor learning is defined as the acquisition of a new skill or behaviour through practice which results in a change in the individual's ability to perform a movement (Schmidt & Lee 2011). The degree of improvement is thought to be dependent on the amount of practice (Krakauer 2006) and VRT offers the opportunity to complete repetitive movements/task practice in a motivating, engaging manner (Levac et al. 2012, Tatla et al. 2013). Key principles should be followed

to enhance learning, these include the incorporation of rest periods (distributed practice), feedback of results, task variability and random ordering of tasks to allow problem solving (Krakauer 2006). However, it is noted in a study by Bonney et al. (2017) in 111 children with DCD that both repetitive practice and varied practice in a VR environment resulted in acquisition of motor skills. It is also suggested that children may require longer periods of practice with feedback reducing more gradually compared with young adults (Sullivan et al. 2008). Depending on the type and intensity of VRT, these principles of learning could be incorporated in VRT rehabilitation programmes. VRT also offers the potential to mimic movements more relevant to day-to-day function than static based exercises (Warland et al. 2019). Additionally, VRT provides an enriched environment which is thought to optimise the context for learning (Morgan et al. 2015). Levac and Jovanovic (2017) also suggest that there is increased retention of skills with physiotherapy in a virtual environment highlighting that virtual reality offers abundant visual and auditory feedback whilst completing goal orientated tasks. In addition to providing frequent task practice and goal orientated therapy in an optimal environment, VRT can also provide feedback directly which may modulate skill acquisition and retention (intrinsic feedback) and this could be supplemented by physiotherapist feedback (e.g. extrinsic or augmented) (Kitago & Krakauer 2013). The role of the physiotherapists in delivering VRT has been demonstrated to be important with increased improvement in outcomes when there has been direct therapist supervision during VRT play (Hickman et al. 2017).

Overall, whilst VRT offers a context to theoretically promote motor learning (Cheung et al. 2014), it remains unclear what dosage (intensity/frequency of intervention) should be used (Levac et al. 2015).

Gaming concept

VRT is often inherently linked with game play but the concept of VRT and game play are dissociable concepts. Games are typically thought to involve a purpose and reward (e.g., points or feedback), follow rules, and may involve competition or other players (Sailer et al.

2017). Physical games may act as rehabilitation (e.g. dance off, throwing to target games) without any virtual reality, and VRT may provide rehabilitation without any game play (e.g. just repetitively copying movements of a virtual actor or exploration without any reward or points scored for success). Therefore, game design (and subsequently game choice) for physiotherapy may be an important factor in rehabilitation.

To optimise principles of motor learning, effective game choice should offer a level of randomness and variation that challenges and requires a range of motor responses, change in difficulty based on improving performance and also an adaptive response to worsening performance to avoid loss of motivation (Krakauer 2006). Specific game choice influences motivation levels during VRT, e.g. football game increased motivation when compared with a navigation game (Brutsch et al. 2011). Gaming therefore offers an advantage in rehabilitation by providing a motivation, reward, cognitive orientation and intention to undertake a movement as opposed to passively completing movements (Bonney et al. 2017). This links with the theory of motor learning where it is thought that intentional and cognitively orientated tasks need to be undertaken for improvements to occur and transfer to everyday use (Krakauer 2006).

Due to the differing principles of gaming and VR it is therefore not clear if the effectiveness of VR is due to the visual and tactile environment on inducing brain changes together with massed practice, or due to the gaming aspects in particular uses of VRT (Cheung et al. 2014).

Motor Learning specific to cerebellar impairment

General principles of motor learning have been introduced in the previous section, but it is important to consider how damage to the cerebellum may influence motor learning and therefore rehabilitation. Motor learning has previously been described as the acquisition of a new skill through practice which is retained, e.g. across therapy sessions (Schmidt & Lee 2011). There are three forms of motor learning; error based (supervised) learning,

reinforcement (reward based) learning and unsupervised learning (Wolpert et al. 2001); this is illustrated in Figure 7.1. Reinforcement learning refers to situations where individuals can explore different strategies to arrive at a solution on their own using intrinsic or reward feedback, that is, those actions which lead to success are reinforced (Kitago & Krakauer 2013). Whereas in error-based learning individuals use systematic feedback to evaluate and correct errors during task performance to improve the result (Ioffe et al. 2007). This could be related to traditional NDT based therapy where therapists provide regular feedback and facilitation to guide trajectories of movement.

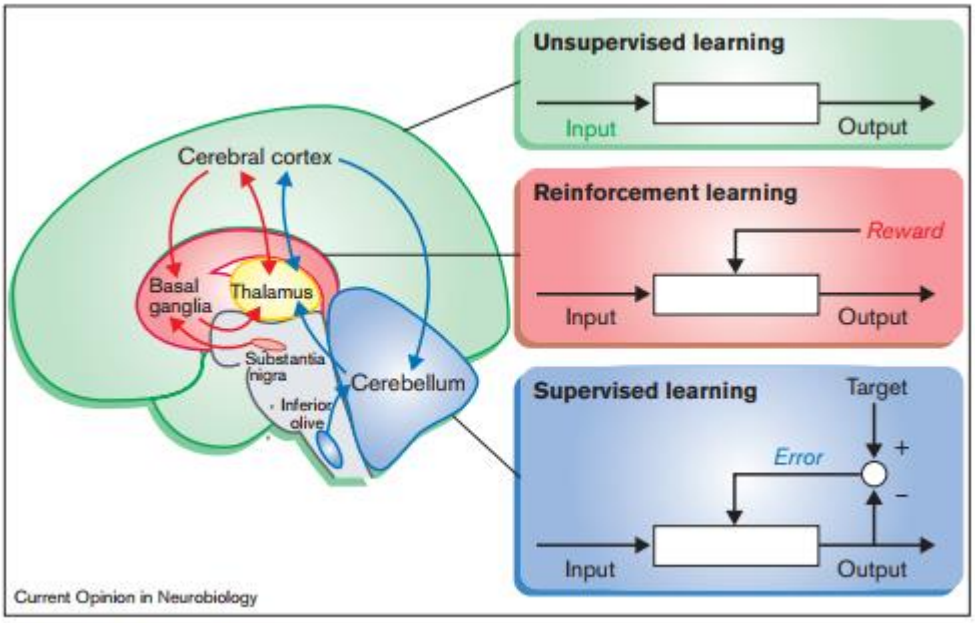


Image freely available from [The basal ganglia, habits and the organizational survival | by Alfonso Fernández | Medium]

Figure 7.1 Types of learning

Cerebellum volume has been linked with motor skill acquisition (Raz et al. 2000), specifically it is thought that people with cerebellar damage have problems with error-based learning (Morton & Bastian 2006). This is potentially due to the cerebellum having a role in estimating error signal, therefore, if there is damage to the cerebellum the ability to learn by error-based learning is impaired (Ioffe et al. 2007). This has been demonstrated in participants with a variety of neurological pathologies (stroke, Parkinson's Disease and Spinocerebellar

atrophy (SCA)) where participants with postural control problems due to cerebellar damage (SCA) demonstrated the worst learning across all three participant groups during an error-based learning task (Ioffe et al. 2006). However, reinforcement learning may be partly preserved after cerebellar damage (Therrien et al. 2016). This is potentially explained as reinforcement learning may function independently of cerebellar processes relying on pathways involving the basal ganglia (Schultz 2006). As initially mentioned in Chapter 3, Therrien et al. (2016) demonstrated in adults with genetic ataxia that better retention of skills was shown with reinforcement learning compared with error-based learning. Therefore, it would seem appropriate to use this principle to assist with learning and retention of skills. Considering balance skills in particular in healthy adults, it has been shown that learning a balance task over 6 weeks (45 minutes per session) using a reinforcement learning model (i.e. verbal feedback on outcome only) resulted in changes in frontal grey matter indices, more than the cerebellum on MRI imaging (Taubert et al. 2010). This study shows that a balance learning task makes use of frontal lobe planning skills and gives a theoretical justification why a reinforcement learning orientated rehabilitation strategy could still work on balance improvement even where cerebellum damage is present.

VRT with a gaming paradigm embodies the principles of predominantly reinforcement-based motor learning, which may therefore be of value in children with cerebellar ataxia, although potentially also error based supervised learning may be present in some games.

Despite potential to influence motor learning there is conflicting evidence regarding formal confirmation of neuroplasticity (defined as changes in neural organisation associated with intense repetitive skill practice/modifications of movement patterns (Berlucchi & Buchtel 2009)) associated with VRT. Sin and Lee (2013) suggest there is MRI evidence of cortical reorganisation after VRT, whereas Laver et al. (2011) report there is only modest evidence of neuroplasticity because of VRT. Golomb et al. (2010) observed increased activation of the primary motor cortex and cerebellum in 3 children (aged 13-15 with hemiplegic cerebral

palsy) following a three-month programme of VRT home training alongside functional upper limb improvements. A study in participants with multiple sclerosis (36 adults, cross over design) reported increased structural integrity of the superior cerebellar peduncle (and balance improvements) following a 12-week Wii programme (Prosperini et al. 2014). Evidence to suggest that VRT interventions result in cerebellar plasticity challenge the view that rehabilitation strategies have no direct effect on the cerebellum. Imaging analysis also helps provide an understanding of the capacity of the cerebellum to respond directly to rehabilitation interventions (so called restorative rehabilitation) and therefore would be of value in future studies in children with primary cerebellar lesions.

The mechanisms of motor learning that are retained in cerebellar ataxia are still an area of active research. However, what is known so far suggests that VRT and games can provide a potentially useful intervention in the rehabilitation of ataxia because they address the key neurophysiological deficits and the theoretical needs of providing a sustained improvement in motor skills.

7.1.3 Use of the Xbox in physiotherapy practice

The Xbox Kinect is one form of VRT that has been used as part of physiotherapy intervention. Indeed, it was the choice of intervention in the study by Ilg et al. (2012) which is one of the larger studies examining physiotherapy intervention for children with (a genetically inherited) ataxia (from a genetic cause). It is one of the most common (alongside the Nintendo Wii) commercially available options to use in a physiotherapy setting as it can be purchased easily from the high street at a relatively low cost compared with bespoke options, and therefore can also be used both within the clinical and home setting. Commercial (off-the-shelf) VRT options often offer more game choice and increased complexity of graphics than bespoke rehabilitation VRT. The Xbox Kinect unlike the Wii does not have a controller and therefore can be used hands free which may be of benefit particularly if a child has dexterity problems. It uses vision-based body tracking using

computer vision (via and infra-red camera) to track human motion in 3D (Morrison et al. 2016). Most games typically generate an avatar on the screen which provides feedback to the participant. Some games may provide more precise visual feedback of body position and limb arrangement than others. Games can be task driven and require problem solving with a variety of visual and auditory feedback generated, along with recognition of performance e.g. collecting points/medals. Games which might target balance can also be played without the use of a balance board (which limits the participant's ability to move to adjust to game play) but do require adequate floor space to play.

Due to the advantages of using the Xbox Kinect in the clinical setting its use has also been specifically discussed by a group of clinicians based in the USA and Canada working in neuro-rehabilitation with the aim of helping clinicians to pick appropriate games relevant to their patient population. The KWiC Framework (Kinecting with Clinicians Resource, Levac et al. 2015) forms part of the group's (Kinecting with Clinicians) work which is a resource available for clinicians to allow game comparison and to select optimum game choice for the target motor deficit. It is an appropriate structure for any VRT game evaluation so could be applied other gaming systems. This document (Kinecting with Clinicians Resource, Levac et al. 2015) helped to frame the feedback received from physiotherapists at the workshops and was used alongside the families' feedback as discussed later in the chapter to provide additional insight.

Chapter 7 Part Two; Workshops exploring VRT

7.2 Research question

What are the most appropriate virtual training games to use in Phase 4 of the study (the feasibility RCT)?

7.3 Aim

The aim of this study (Phase 3) was to inform the choice of video games to be used in the feasibility RCT (Phase 4).

7.4 Specific objectives

The objectives of Phase 3 were to:

1) identify appropriate VRT games with a particular focus on Xbox Kinect games (as this type of virtual training is readily available and has been successfully used in previous trials with participants with ataxia); and
2) explore additional software that can link with the Kinect that would be child friendly, appropriate to use in this population and enable progress/compliance to be recorded.

7.5 Study design

Two workshops were used to collect data to answer the research question. Workshops provide a forum for discussion alongside opportunity for practical application/demonstration of activities (Spagnoletti et al. 2013). Workshops typically involve small groups with a focus on engaging participation from attendees to allow discussion and facilitate problem solving in order to achieve the aims of the workshop (RSPSC 2017). This was suitable for the specific objectives of this study where it was important to enable participants to try the VRT games available at the workshop and to offer feedback. It allowed children, their families and physiotherapists to discuss their thoughts about the games together whilst offering the advantage that physiotherapists could see children with balance problems trying different gaming applications. Two workshops were planned to allow opportunities for a larger number of participants to attend depending upon their education/work commitments whilst ensuring the specific objectives of this study were met. This also enabled the workshops to

include different gaming experts who shared their innovative products/ideas on incorporating VRT into clinical practice. They were present at the workshops in the capacity as demonstrator/expert of their available software.

7.6 Workshop plan/development

In order to ensure the workshops were effective a number of steps were undertaken in the planning process. In the first instance advice was sought from both within and external to the supervisory team from clinicians and researchers with experience in conducting workshops. This gave an understanding of the need to outline the objectives for the workshops, encourage active participation whilst varying activities and also summarise the session ensuring the participants' feedback has been understood correctly. This information was supplemented with literature sourced from different health professional groups who have produced guidelines and tips for conducting effective workshops (e.g. the toolkit from the Association of American Medical Colleges and Royal College of Physicians and Surgeons of Canada (RSPSC 2017).

A workshop plan was then developed which outlined the timetable for the sessions with incorporation of breaks considering there would be differing ages of children attending (Appendix 14). The introductory part of the workshops allowed time for greeting participants and the consent process, with a breakout table for arts and crafts/activities to ensure the younger children had access to activities to occupy them if they were waiting. The group were then informed of the aim of the workshop and an ice breaker session followed which consisted of all participants making their own name badges which used pictures/stickers of different characters/activities which could be linked with potential games. This started discussion on activities in a relevant way that the participants enjoyed.

A variety of workstations allowed participants to try both commercial Xbox games and experience the bespoke software shown by the rehabilitation gaming companies. Time was

allowed for feedback with flexibility built in to expand or collapse the stations dependent on number of attendees. Facilitators were delegated to different workstations in advance to allow preparation in their particular area.

The workshops closed with the opportunity to summarise feedback and confirm the information provided by participants. Certificates were presented to the children for attendance.

Facilitator guidance was produced (Appendix 14) to ensure the overall objectives remained at the forefront throughout the workshops. The key areas of achieving the objectives were reinforced considering; level of engagement, practicality of use in the home setting, practicality of use in the clinic setting and utility regarding therapeutic value. Prompts were also provided including topics/questions to promote relevant discussion at particular stations.

7.7 Workshop preparation

The Innovation Hub at the host NHS Trust was used as the location of the workshops as it offered a large space with different breakout rooms with access to IT support. Working with the Innovation Hub in the planning stage also generated discussion regarding appropriate contacts for gaming experts to collaborate as part of the workshops. Using these contacts and considering the different virtual training options noted by therapists in the e-survey, four companies/products were identified (MIRA, Virtual Rehab, GRAIL system and Tyromotion). These companies were then researched (to source availability, cost, population of use and paediatric game choice) via the internet and then through email contact. The GRAIL system and Tyromotion did not currently have suppliers in the UK and therefore were not considered further for involvement in the workshops. Both MIRA[4] and Virtual Rehab[5] offered bespoke virtual training rehab software packages that use the Xbox Kinect and had or were

[4] http://www.mirarehab.com
[5] https://evolvrehab.com/virtualrehab/virtualrehab_body/

in the process of developing paediatric games (MIRA has tailored paediatric games following work with therapists and children in a regional paediatric therapy service as part of the IPlay Project). Therefore, both companies were contacted and were sourced to attend a workshop each to allow opportunity for participants to try bespoke virtual training rehab options.

A list of equipment required for the workshop was noted when the workshop plan was developed and relevant equipment sourced in advance (e.g., Xbox and Kinect sensors, variety of Xbox games, flip charts/pens, stickers, audiorecorders). Facilitators with experience conducting workshops and/or with an interest in physiotherapy for children with balance problems were contacted when the workshops were being designed. This allowed enough facilitators to ensure the participants were able to complete all the activities and move through the workstations with no delays whilst capturing all their feedback.

7.8 Target population

The target population was children who had undergone surgical management of a PFT aged 4-18 years of age (see inclusion criteria 7.11.1), their parents, and physiotherapists with an interest in this area. It was important to have children, their parents and physiotherapists to enable the specific objectives of the workshops to be met. The target was to achieve a mixed age range of children attending to help with selection of games that would suit all potential participants in Phase 4 of the study. Physiotherapists with an interest in this area working in both the acute and community setting were also considered as the target population.

7.9 Ethical issues

Phase 3 of the study was submitted as a joint ethics application with Phase 4 of the study as advised by local research and development teams to minimise any delays between the two phases (with the acknowledgement that an amendment could be submitted, as

required, if the protocol of Phase 4 of the study was refined by information from the workshop).

The study was granted ethics approval through Edge Hill University FREC Committee (FOHSC 189) (Appendix 15). It was then subsequently submitted for REC and HRA approval via the IRAS process (IRAS ID 227917) in October 2017. As Chief Investigator (CI), I attended a REC committee meeting in November 2017 with Professor Barry Pizer. Feedback from the REC committee was favourable, subject to clarification from MHRA regarding the use of the X Box Kinect. Therefore, the start of the study was slightly delayed whilst awaiting a decision from MHRA. During this time there was ongoing communication with the HRA regarding minor amendments to participant information/consent sheets and the Statement of Activities. REC and HRA approvals were subsequently received at the end of February and beginning of March 2018 respectively (Appendices 16 and 17).

Ethical issues concerning informed consent, time demands, and risks to participants were considered throughout the design and conduct of Phase 3. Regarding informed consent, a variety of different participant information sheets were designed to enable children of different ages and cognitive ability to be informed about the study (Appendices 18-22). Assent and young person and parent/clinician consent forms were also produced (Appendices 23-26). These were designed with guidance from the research team and parent feedback, and a parent representative on the study steering group committee also provided feedback on this documentation. Children and their families had a minimum of two weeks to consider their involvement in the workshops also before deciding whether to take part.

The time commitment involved in attending the workshops was made clear both on the written information and in discussions with the potential participants, and participants were offered the option to attend one or both workshops. One workshop was carried out on a day when a busy neuro-oncology clinic was also being held to potentially allow families to attend

the workshop when they were already visiting the hospital. Standard travel expenses were also available for participants taking part in the workshops. No significant risks to taking part were highlighted although physiotherapists were available to supervise participants who were trying out the VRT.

7.10 Research governance issues

Data protection and confidentiality issues were also considered. Personal addresses of the children/their families were used to send out specific participant information sheets/workshop invites to interested participants. However, these details were only available to the direct research team and the information was securely stored and available only via password protected NHS computers.

Considering the actual conduct of the workshop it was made clear to all attendees that participants may share names and information during the workshop. Participants were reminded of the importance of confidentiality and ground rules were agreed by all participants not to reveal shared information outside the workshop without direct permission. Any notes made from the workshops were pseudoanonymised, with the use of unique randomly generated codes as identifiers of individuals during transcription. Participants who attended the workshops were clearly informed that feedback given by themselves during the workshops may be recorded and used for future research and may be published, however, no identifiable data would be shared outside of the workshop.

The site file contained limited personal details and was securely stored according to local policies at the host NHS Foundation Trust. The supervisory team via the lead researcher had access to anonymised data which was not available to anyone else. Data analysis took place at the host NHS Trust and EHU.

General Data Protection Regulation (GDPR 2018) came into effect during this study period and therefore a new GDPR compliant information sheet was also shared with the

participants as advised by the host NHS Trust research and development team (Appendix 27). Data will be securely stored for 10 years after the research concludes in line with this policy.

The study was monitored by the supervisory team and there was additional external oversight from the NIHR.

7.11 Recruitment

7.11.1 Inclusion criteria

1) Children aged 4-18 years and their parents who have been managed by the neuro-oncology team at two Tertiary Paediatric Neurosurgery/Oncology Centres in the North of England for a PFT.
2) Physiotherapists with an interest in neuro-oncology/virtual training.

7.11.2 Participant recruitment - children and their parents

Initial plans were to include all children aged 4-18 who had been managed under the neuro-oncology team for a PFT at two Tertiary Paediatric Neurosurgery/Oncology Centres in the North of England. However, due to delays in opening the second site, children and their parents from the host site only were eligible to take part. Flyers were posted in the neuro oncology clinics at the host site (Appendix 28). If the children expressed an interest in the workshops they were given more information by the CI and sent out written participant information sheets (Appendices 18-22). If the children and their parents indicated they wanted to take part then a specific invitation for the workshops with details of date, time and location were also subsequently sent via post (Appendix 29).

7.11.3 Participant recruitment - physiotherapists

Physiotherapists with an interest in this field were also invited to take part in the workshops. Flyers (Appendix 30) were sent out to acute therapists at both Tertiary Paediatric

Neurosurgical/Oncology Centres, and to eight local community physiotherapy bases which are common onward referral bases for children with ataxia following PFT after their transfer from acute care across the North of England. If physiotherapists expressed an interest in the workshops, then participant information sheets (Appendix 22) were sent out followed by a specific invitation for the workshops, as appropriate (Appendix 29).

7.12 Data analysis

Preliminary analysis was conducted within the workshops by the participants (through ranking the games played, identifying the biggest challenges and most attractive attributes). Participant driven analysis included ranking of and rationale for:

- Level of engagement;
- Practicality of use in the clinic setting;
- Practicality of use in the home setting;
- Utility regarding therapeutic value; and
- Positive aspects, potential barriers and solutions identified by participants to using the technology

Following the workshops, the participant-driven analysis was supported by the researcher using thematic analysis to add depth (Braun & Clarke 2006a). As CI, I transcribed all audio-recorded discussions. These were analysed along with other data sources such as words and phrases recorded on flip charts. Initial examination of the collected data was used to gain a general impression before the data were repeatedly examined. The data were subsequently coded and the themes were documented (Braun & Clarke 2006 a & b).

The analysis of these data informed Phase 4 of the study, specifically with regard to the selection of games for the virtual training intervention. The KWIC (Kinecting with Clinicians) Framework was used to further review specific games that were ranked highly from the

workshops across all aspects of engagement, practicality and therapeutic utility to finalise game choice.

7.13 Results

7.13.1 Participant demographics

Sixteen families and six physiotherapists initially expressed an interest in the workshops and were therefore sent further information regarding the sessions. Six families subsequently planned on attending the workshop and were sent specific invitations. Ultimately five families and five physiotherapists attended the workshop. All names have been changed for the purpose of maintaining anonymity.

The same selection of commercially available Kinect games were offered at both workshops and encompassed different domains of adventure, sport and dance.

The first workshop was held in April 2018 and involved three physiotherapists (two from a community setting (Sian, Bethan) and one from an acute setting (Lucy), two children (Bella age 10 years and Lily age 7 years), and their parent/parents (Linda, Jo, Don) and a further parent (David), whose child was unable to attend as they were unwell on the ward. The participants were able to try commercial Xbox Kinect games and also experience the software presented by Virtual Rehab company.

The second workshop was held in May 2018 and involved two physiotherapists (Lucy, Amber) (both from an acute setting, one who had attended workshop one) and two children (Orlan, aged 8 years, Rory, aged 17 years) and their parents/older sibling (Katherine, Ian, Ryan). As in the first workshop, the children were able to try commercially available Xbox Kinect games but in this workshop they also experienced using MIRA software.

Across the two workshops the age range of the children/young people who participated was between seven and seventeen. Three of the children (Bella, Rory, Orlan) were mobile either independently or with supervision, the fourth child (Lily) was able to stand with assistance.

7.13.2 Level of engagement

Participants were asked to rank each game they played on a scale of 1-10, with 10 representing the most fun/interesting. The games that were consistently ranked the highest by all participants (scoring 8 or above) are presented in Table 7.2. When asked to rate whether they preferred 'commercial Kinect games' or the bespoke companies' software all the children chose the commercial Kinect games, although physiotherapists and parents noted both positive and negatives of all types of software and these are discussed further in 7.13.3.

Table 7.2 – Games ranked 'most fun' by participants

Commercial Kinect Games	MIRA	Virtual Rehab
Reflex Ridge (Kinect Adventures) Jetski (Kinect Sports Rivals) River Run (Kinect Adventures) Soccer (Kinect Sports) Mountain Gold Rush (Carnival in Action)	Space Ship Seasons Izzy Bee	Boxing Weightlifting

Parents commented that the children appeared engaged in the games. One mother commented *"she's moving but doesn't know she is doing physio"* (Linda), another father agreed *"it's just fun – that's half the battle isn't it"* (Don). Another father stated, *"it's all about having fun, she likes the boxing game"* (David). Parents agreed that trying to complete home exercise programmes can be difficult and suggested that videogaming may increase participation. One mother reported *"making him do OT/Physio at home, a nightmare – think he would do these at home, 100%"* (Katherine). This was supported by another family who explained that *"physio would be classed as a task, whereas this would be a game"* (Ryan).

Physiotherapists also observed that the children sustained their interest in playing the games noting that *"[river run] engaged her, she felt like she was achieving"* (Sian).

Participants ranked games lower that they found too difficult to achieve. One teenager commented *"I didn't like the jumping games, did I come last in that one?"* (Rory) another child reported a similar reason *"felt wasn't good at it, that's why ranked lower"* (Lily).

7.13.3 Practicality of use in the clinic setting

Participants were asked to rank how easy each type of gaming would be to use in terms of order of practicality/ease of use for both clinic and home setting, see Table 7.3.

All participants ranked using the Xbox Kinect with commercial games the most practical, except for physiotherapists suggesting that MIRA would be easy to use in the clinic setting with acute patients. Physiotherapists noted that *"[MIRA] very easy to play and calibrate"* (Lucy) and that it could be used in children with a range of difficulties as it was *"easy to initiate if you have movement disorders"* (Amber). They also found being able to build a bespoke programme of games for the child as a positive attribute as *"MIRA can build a programme – no lag in between"* (Amber). Physiotherapists commented on both bespoke options (MIRA and virtual rehab) that they could see patient outcome/compliance which was seen as a positive.

Table 7.3 – Type of gaming ranked according to practicality by the participants

	Practicality in the clinic setting (ranked most easy to more difficult)	Practicality in the home setting (ranked most easy to more difficult)
Children	1. Xbox Kinect commercial games 2. MIRA 3. Virtual Rehab	1. Xbox Kinect commercial games 2. MIRA 3. Virtual Rehab
Parents	1. Xbox Kinect commercial games 2. MIRA 3. Virtual Rehab	1. Xbox Kinect commercial games 2. MIRA 3. Virtual Rehab
Clinicians	1. MIRA 2. Xbox Kinect commercial games 3. Virtual Rehab	1. Xbox Kinect commercial games 2. MIRA 3. Virtual Rehab

They were also asked for any further comments on how practical (how easy) VRT overall would be to use in the clinic setting. All participants' comments were thematically analysed. Three themes were identified: space, technology, and child/patient ability.

Participants noted that *space* was important as a clear area is required to use gaming as part of physiotherapy treatment with both physiotherapists and families acknowledging that VRT could be used only *"if there is the space available"*. Physiotherapists acknowledged if there was a dedicated space with the equipment already set up then they would be more likely to use it *"otherwise it's just the set-up time, especially if you are not that familiar with it"* (Bethan).

The participants commented on factors about the *technology* involved. Positive comments, based on their observation, were noted with one physiotherapist reporting *"it was easy to calibrate"* (Sian) and another mentioned *"sensors are better than holding something"* (Amber). The fact that the Kinect is not restricted to the use of consoles and other equipment (e.g. balance board as used with the Wii) was raised by another physiotherapist who explained *"we have the Wii but they [patients] find it difficult to keep on the balance board, can be anxious to move to much if they are unsteady as it is a small platform"* (Bethan).

The participants also considered that *children's ability* could influence the practicality of the use of VRT in the clinic setting. Physiotherapists felt they would benefit from having more knowledge about the games available so they could select particular games according to their patients' needs. One physiotherapist suggested that VRT would be more practicable if there was *"a menu of which games target specific activities – balance, stamina etc."* (Amber). It was noted the bespoke gaming companies offered more options to tailor the games to individual patient need e.g., to play in a sitting position or adapt if there was any asymmetry. One father commented his daughter *"couldn't do that now, can't stand much at the minute, but she could do that one as could pick height of targets"* (David). Another mother commented that her daughter *"can't use both sides [of body] well at the moment,*

would need something that could adapt" (Jo). Child/patient specific presentation was thought to influence how practical virtual training would be to use in the clinic setting with physiotherapists noting the choice of training would *"need to be able to customise with patient information".* However, there was general consensus that off-the-shelf games would be practical to use in the clinic setting particularly for children who were able to stand independently. One physiotherapist commented *"for mild balance problems commercial games would be suitable and there are choices of games for all ages"* (Lucy).

7.13.4 Practicality of use in the home setting

Participants were asked to consider the practicality of using VRT in the home setting. Ranking of most practical games is illustrated in Table 7.3. Comments raised regarding overall practicality of use in the home setting were all considered and thematically analysed. Four themes were identified (space, technology, child ability and home exercise/therapy programmes). The first three themes are the same as those identified for practicality of use in the clinic setting, albeit with a slightly different emphasis.

Participants again repeatedly noted that an appropriate *space* would be required to carry out the training. One teenager (Rory) when asked if they felt they could do it at home reported *"yes if you have the space".*

Technology factors were commonly raised by both physiotherapists and the families. Physiotherapists anticipated that families would be able to use the software at home, one stated it *"would not require that much info for family to use at home"* (Amber). Two fathers also reported they had similar technology at home demonstrating familiarity with the software, one father stated that they *"got an Xbox but haven't tried the Kinect"* (Ian), another commented *"we have the Wii but haven't used this [Xbox]"* (Don). Parents appeared pleased that the games were readily available to access, one mother enquired *"can I buy this one, I want to get this one for her"* (Linda).

Participants also considered the *child's ability* when discussing practicality of use in the home setting. There was discussion around physical ability similar to that reported in the practicality in the clinical setting section, but also parents raised concerns that the instructions might at times be too difficult for their children to follow. One mother reported *"she [child] can't read, are there any verbal instructions? She wouldn't be able to do this"* (Linda). Physiotherapists also concurred that verbal instructions would also be beneficial as it *"would be better if verbal instructions if reading ability not good"* (Sian).

Participants also suggested that using virtual training at home might be a better way to encourage participation in a *home exercise* programme. This mirrors feedback when engagement was discussed (7.13.2). Parents suggested it would be a way to incorporate activity and complete their home exercise programme, one father noted it *"would be easy enough to do, would keep off iPad and keep entertained for long enough"* (Don). Another father commented *"it would be good to do for physio at home, better than normal physio, would do it as [involves] a screen"* (Ian).

7.13.5 Utility regarding therapeutic value

Physiotherapists were asked to provide feedback on therapeutic value of the VRT completed at the workshops. To focus the conversation the physiotherapists who were present at the first workshop alongside facilitators (who included two physiotherapists and a consultant paediatric neurologist) discussed which elements of the KWIC resource they felt were important to consider. The following domains were chosen in order to gather further information during the workshops; age range of the games, stability/playing position, accuracy/co-ordination, cognitive, feedback (provided by game), and progression. Table 7.4 illustrates the feedback provided by physiotherapists across both workshops for each domain.

Table 7.4 Physiotherapist feedback on therapeutic utility

Domain	Feedback listed on flip charts (Clinicians n=5)		
	Commercial Kinect Xbox games	Virtual Rehab gaming	MIRA gaming
Age range	• 'good choice to interest' • 'variety of age ranges' • 'very interactive, fun'	• 'could be used for any, however games may get boring quicker for older children' • 'all include younger options'	• 'dependent on games, ?5-18
Stability/Position	• 'river rush, just dance, ice cubes – side stepping' • 'some involve jumping'	• 'accurately predicts body position' • 'able to use in sitting and standing' • 'can challenge balance'	• 'accurately maps body position' • 'takes time to accurately match body – but seems accurate once set up'
Accuracy/co-ordination	• 'river rush – doesn't require too much accuracy' • 'more global skills than other system (virtual rehab) which can be more specific to skill/tailored patient' • 'difficulty with reactions for ralleyball'	• 'can be adjusted to suit ability of patient' • 'some of the games do require accuracy' • 'running – low accuracy needed'	• 'boxing and target game – high accuracy needed' • 'good as able to adjust settings to match child's ability of coordination'
Cognitive	• 'good assessment of visual skills'	• 'can combine physical challenge with cognitive challenges' • 'can work on memory with physical' • 'some games are more cognitively biased'	• 'awareness of left and right – colour coding'
Feedback	• 'video feedback/record' • 'scores/stars positive feedback' • 'Able to do multiplayer'	• 'gives variety of feedback data relevant for child and clinician' • gives feedback on data including duration/range of movement'	• 'out of 3-4 games seen nice variety of difficulty and skills required' • 'able to adjust settings to accommodate different abilities'
Progression	• 'game [river rush] keeps going even if crash which is good (Wii doesn't)'	• 'able to adjust tolerance/accuracy of exercise as a % • 'able to increase progress game – easy – hard'	• 'target game – increased speed of targets' • 'able to progress in different ways – just R [right] or L [left], UL [upper limb] or LL [lower limb]'

Task specific training	• 'yes – unable to transfer weight to left therefore target this for treatment and reassess' • 'reaching to target'	• 'sit to stand games' • 'able to work on task specific training i.e. reaching - ataxia'	• 'different games work on different activities i.e. sit to stand'
Balance	• 'river rush and just dance [work on this]'	• 'balance incorporated into lower limb exs [exercises] e.g. balance in 'standing whilst doing hip abduction' • 'side tapping e.g. American football'	• 'target game incorporates side stepping and SLS [single leg stance]'

Overall physiotherapists noted that the games could suit a variety of ages and offered the option to complete these in different positions including more challenging postural sets. The ability to offer feedback was praised. This feedback ranged from a more clinical focus with bespoke rehabilitation gaming options (e.g. percentage of targets reached with left upper limb), to child focused (e.g. collecting stars for off-the-shelf games). All types of games offered the opportunity to progress either within the game itself or moving to a higher entry level. Physiotherapists felt that VRT, dependent upon game choice, provided a setting to use both task specific training and balance training as part of physiotherapy management.

Children and their parents were also asked if they wanted to comment on therapeutic value. The question was framed as 'will it help me (or my child)'. A range of comments were noted but no strong themes were identified although participation, the adaptability of games and ability to target specific problems (e.g. balance or fitness) are reported below.

Parents suggested that using VRT might encourage *participation* through the opportunity to do multiplayer games that could build confidence to try other activities such as adapted sport/dance. One mother noted VRT *"helps join in with others with play – might encourage participation outside of physio"* (Linda). Parents also noted that different games were *adaptable* and felt they did *target specific problems* such as balance. One father stated *"good, works on balance"* (Don), and one girl (Rory) reported "spaceship game good for

people who can't sit still". The children reported which games they felt had worked them hardest, e.g., "*shape up – work hardest, river rush – involves jumping"* (Orlan), and both physiotherapists and parents agreed that the commercial Kinect games in particular would also work on fitness and stamina. One father noted that *"off-the-shelf games – more cardiovascular workout"* (Ian), physiotherapists agreed that these games were *"good exercise, increased heart rate"* (Bethan).

7.13.6 Positive aspects, potential barriers/solutions

Although the majority of positive aspects of VRT were raised within the sections on engagement and practicality, three further factors were raised by participants during the workshops. Parents and physiotherapists repeatedly mentioned the advantages of games (particularly commercial games) which did not stop if the child could not achieve something (e.g., they continued to play if the player 'crashed' or could not reach a specific target). Participants felt this would motivate the children to carry on with the game and potentially reduce frustration. One physiotherapist commented *"raft doesn't stop even if crash – there is no negative feedback"* (Bethan), parents agreed with this with a mother explaining that her daughter *"can't see if she is doing it wrong therefore she just carries on"* (Linda). Parents also thought that using VRT at home might encourage siblings to complete activities together although there was caution that if one sibling was much better than another it might be discouraging. One mother remarked *"siblings would do it – only thing is if [child post PFT] see they are better – might not want to do it"* (Linda). Physiotherapists also noted that the use of VRT may be advantageous in terms of *"freeing up"* clinical time. They suggested that if a programme of games had been selected then a block of treatment could be delivered by a therapy assistant followed by reassessment by a qualified member of staff thus allowing increased clinical capacity.

The potential barriers to using VRT all centred on the use of technology. Concerns were raised about the ability to set up the equipment and trouble shoot it, if necessary. The

acknowledgement that technology changes quickly and that the chosen software can become outdated were also noted.

Overall, the participants were positive about using VRT in clinical practice in both the home and clinical settings. Physiotherapists felt that VRT was of particular value to children with ataxia due to the nature of their problem, one physiotherapist offered a summary *"children with ataxia like to move – don't like activities where they stay still, this means they can do that"* (Lucy).

7.13.7 Synthesis of results

All aspects of engagement, practicality, and therapeutic utility were then considered by the research team to help confirm the intervention protocol for Phase 4 of the study. Due to the availability (accessible on the high street at relatively low cost) and positive feedback, commercial Kinect games were selected as the intervention of choice for the RCT. Games ranked the highest by the participants from the workshops were subsequently further analysed by the research team according to the KWIC framework (Levac et al. 2015) to help specify particular game choice for the intervention in Phase 4. An example of this for one game – Kinect Sports - with its six sub games is illustrated in Table 7.5 (further details are in Appendix 31).

Table 7.5 KWIC Framework – game analysis

	Kinect Sports					
	Soccer (MS) (Participant top ranked)	**Bowling (MS)**	**Beach Volleyball (MS)**	**Boxing (MS)**	**Table Tennis (MS)**	**Track and Field (MS)**
Game description	Player is in football match environment. Player passes and shoots by stepping and kicking, and then defends passes/acts as	Player is in bowling venue. Bowls ball, playing against computer or other players	Player completing a game of beach volleyball. Player serves by using upper limb, and jumps for jump shot	Player is in boxing ring and competes in 3 rounds of boxing. Player punches high and low using upper limbs and blocks shot by covering	Player competing in table tennis match. Player serves using upper limbs and directs shots with trunk/arm positions	Player competes over five events. 1) Sprint (running on spot). 2) Javelin (runs on spot and release javelin with upper limb). 3) Long jump (run on spot and time jump). 4)

	goalkeeper also			face with arms		Discus (time upper limb movement to release). 5) Hurdles (run on spot then time jump to clear hurdle)
Age	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)
Flexible entry	Yes (Beginner, Intermediate, Advanced)	Yes (Beginner, Intermediate, Advanced)	Yes (Beginner, Intermediate, Advanced)	Yes (Beginner, Intermediate, Advanced)	Yes (Beginner, Intermediate, Advanced)	Yes (Beginner, Intermediate, Advanced)
Game Start	Player raises left arm. Then uses lower limb to pass to begin match	Player raises left arm. Then player picks up ball to bowl	Player raises left arm. Then play serves by moving arm to begin match	Player raises left arm. Then fight begins	Player raises arm. Then reaches to pick up paddle with arm and serves to begin	Player raises arm. Then event begins with sprint, race starts automatically.
Player/Game driven	Player Driven: Player needs to pass to initiate movement of ball	Player Driven: Player needs to pick up ball to bowl	Player Driven: Player needs to serve to begin game	Game Driven: Fight continues regardless of players involvement	Player Driven: Player needs to serve to continue with their own play	Mixed dependent on event. Races are game driven i.e., continue regardless of involvement. Field events are player driven
Stability	Yes: Standing	Yes: Standing	Yes: Standing	Yes: Standing (OR SITTING only if match has started)	Yes: Standing	Yes: Standing
Mobility	Yes: Arms Legs Trunk Head	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms (Legs) Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk
Agility	Yes: Side stepping	Yes: Side stepping	Yes: Side stepping and jumping	No	Yes: Side stepping	Yes: Running on spot and jumping
Spatial Accuracy	Yes: To direct pass/aim for goal	Yes: To aim ball	Yes: To direct serve/shot	Yes: To direct punch	Yes: To direct shot	Yes: To throw javelin/discus
Game Duration	Consistent	Consistent (fixed number of rounds)	Skill dependent: Shortens	Skill dependent: Shortens	Skill dependent: Shortens	Predominantly Consistent (same number of rounds for each field event. Races time

						dependent on performance)
Cognitive operations	Response selection Planning	Planning Response selection	Planning Response selection	Planning Response selection	Planning response selection	Planning Response selection Switching attention
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Yes: Progress to performing different actions	Not within game	Not within game	Not within game	Not within game	Not within game
Performance Indicator	Game score. Can unlock achievements with overall performance	Score for game. Can unlock achievements with overall performance	Score/result of game. Can unlock achievements with overall performance	Win/lose contest. Can unlock achievements with overall performance	Score of game. Can unlock achievements with overall performance	Time/distance for each event, and points and position given for overall event. Can unlock achievements with overall performance
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments	Overall games typically longer than those on Kinect adventures/Carnival in action therefore suited to more able/older child					Bias on aerobic content. Most physically demanding game

Legend: MS (Multiplayer simultaneously), MT (Multiplayer turn taking), S (Single player)

7.14 Discussion

The workshops provided a unique insight into the views of children, their parents, and physiotherapists on the use of VRT for children with ataxia following surgical resection of PFT.

Overall, there was positive feedback regarding participant engagement reported in the workshops from both parents and physiotherapists. This is reflected in the literature with high adherence/compliance to VRT intervention observed in children with ataxia (Ilg et al. 2012) and children with cerebral palsy (Brien & Sveistrup 2011). Engagement in physiotherapy intervention is particularly important considering one of the underlying aims of neurorehabilitation is to support neuroplasticity through high intensity training. Specifically, children with cerebellar ataxia potentially have difficulties with aspects of motor

learning due to impairment of the function of the cerebellum. People and arguably children in particular with cerebellar disorders may need longer or higher intensity training schedules to learn new skills/show progression (Ilg et al. 2012), or even different game design optimised for what is retained and lost in cerebellar damage. Therefore, finding a way that can motivate and engage children in a repetitive task driven and reinforcement learning approach could be beneficial. VRT is therefore proposed as a way to facilitate rehabilitation, especially intensive repetitive movements that children otherwise might find boring. It is also important to consider that children who have undergone treatment with cancer are known to demonstrate lower physical fitness than their peers, alongside associated problems with bone density (Huang & Ness 2011) and VRT may also offer a potential of improving these problems. Participants reported that they felt off-the-shelf games, in particular, worked on cardiovascular fitness and stamina offering dual benefits for children with PFT.

Participants reported that they felt VRT could be incorporated into both the home and clinical setting. Interestingly physiotherapists noted the benefits of bespoke virtual training and felt this may be advantageous in the acute setting in particular where more adaptation may be required to allow children to play the games (e.g. complete in a standing position or accommodate asymmetry). Children rated commercial games as more fun, this may reflect the more complex graphics offered with these games that the children might be familiar with playing. Most of the parents reported they were familiar with some type of gaming although the model varied. Other studies have varied using both bespoke and commercially available gaming technology with the Kinect and Wii being the most popular off-the-shelf games (Deutsch & Westcott McCoy 2017). Parents and physiotherapists both recognised the benefits of the use of the Xbox Kinect in particular allowing arms to be free without the use of a controller. Maintenance of upper limb freedom is also noted as an advantage in the literature alongside the capability of the Xbox to provide accurate feedback with participants able to observe movement though an avatar on screen (Sin & Lee 2013).

The highly engaging nature of VRT was discussed by participants when considering using the technology at home and the parents reported that using virtual training as part of a home exercise programme may increase adherence. Parents reported how difficult it can be to assist the children to carry out their existing therapy programmes and this is reflected by low adherence to exercise programmes reported in the literature (because of lack of time, fatigue (of the child) and resistance of children to complete their home exercise programme (Maring et al. 2013)). This last element may be influenced by the use of VRT as part of the home exercise programme if it is motivating to play the games.

Despite the positive feedback by participants in the workshops and the emerging use of virtual training in the literature, it is noted that VRT is not actually that widely used as part of routine practice (Glegg & Levac 2017). This is supported by the e-survey (Phase 2 of this study) where virtual training was reported as only the fifth most often used adjunct to treatment. However, in the 57% of physiotherapists who had used VRT, 73% had used this in children with PFT indicating the potential in this population. Barriers to implementation of VRT reported in the literature include lack of time to implement, lack of funds to purchase equipment, lack of treatment space and lack of support for staff (Glegg & Levac 2017). The need for space was observed from both physiotherapists and families at the workshops and physiotherapists did raise concerns regarding technology issues (which is linked to the lack of support for staff observed by Glegg and Levac (2017)). However, lack of time and lack of funding were not discussed by participants in the workshops (although were noted in the e-survey feedback). Within the workshops any concerns were typically individually child focused (e.g. children ranked the games lower if they found them difficult), or parent focused with parents expressing concern about the lack of verbal instructions for specific games and the potential for frustration if their child could not complete the games as well as their siblings. Careful game selection based on game characteristic criteria (e.g. fixed or variable game entry points, stability and mobility requirements, and spatial and temporal constraints)

as also indicated by Levac et al. (2015) could alleviate some of these game-specific and child-specific problems.

There were no significant negative aspects raised about the use of VRT in the workshops. The minimal literature on this element means it is difficult to establish if it is due to poor reporting of any adverse events or an actual lack of negative issues for this type of training. One large study by Hseih et al. (2016) who examined the use of VRT in 101 children with developmental delay did look at psychosocial health and reported that VRT affected physical outcomes only, and there were no adverse effects (they considered aggression, hyperactivity and sleep disorders as possible adverse effects). Although this is encouraging, it may be due to a general lack of reporting, so it is important to report any adverse effects in trials and use quality of life measures as part of the outcome measure selection.

During the workshops physiotherapists raised the potential of VRT as a way to maximise clinical time with the programmes being carried out by physiotherapy assistants. However, it is noted in the literature that VRT with a therapist is reported to result in significantly better outcomes than the use of virtual training alone (Brutsch et al. 2010). This indicates that physiotherapy involvement remains integral e.g. providing specific feedback throughout the training or tailoring game choice according to the child's needs. Therefore, it is proposed VRT is a 'tool' for use by physiotherapists which can be adapted appropriate to children's needs offering an individualised approach whilst not replacing physiotherapy input.

7.14.1 Limitations

Five parents, four children and five physiotherapists attended the workshops though ideally it is acknowledged that a wider collection of parents and children's views from different sites would have been beneficial to further inform the planning of Phase 4 of the study. However, the small numbers attending each workshop enabled children and their parents considerable periods of time to try multiple games with no time pressure. The second workshop was held in the school holidays as the reason most families gave as not being

able to attend workshop one was a reluctance to bring the children out of school. However, it is noted that children who attend regional oncology units come from different geographical areas and even though the second workshop was in half term for one region this was not the same holiday time for other areas.

It is also acknowledged that the game choice at the workshop, although varied, represented a limited preselection of games available from the overall market and alternative games on the market might have been worth considering. However, the preselected game choice was carefully considered and included all games that had previously been reported in the literature (e.g. Kinect Adventures). The selection of games also covered differing domains of sport, adventure and dance and aimed to target a variety of age groups.

7.14.2 Impact on Phase 4

Completion of the workshops provided specific information to inform Phase 4 of the study. Feedback received by the participants confirmed the type of virtual training to use in the RCT, that is, the decision to proceed with the Xbox Kinect with commercially available games. Further participant feedback and subsequent analysis considering the principles of motor learning e.g. feedback, progression, then enabled the selection of specific games to use in the RCT dependent on the child's age and physical/cognitive ability. The workshops supported the ongoing participation of children and their parents in the refinement of the study design.

7.15 Conclusion

In conclusion, five parents, five children and five physiotherapists attended the workshops providing feedback on engagement, practicality and therapeutic utility of using VRT for children with ataxia following PFT resection.

Overall positive feedback was observed regarding engagement with participants also reporting that VRT would be practical to complete in both the clinical and home setting.

Therapeutic benefits of VRT were also reported alongside the need to consider individual children's needs when selecting games and planning treatment programmes. The workshops provided confirmation for the choice of Xbox off-the-shelf games for intervention for Phase 4 of the study and enabled selection of specific game choice for the intervention group protocol.

Chapter 8 – Phase 4 – Feasibility RCT examining the effectiveness of virtual training on ataxia in children (virtual training and usual care versus usual care) following surgical resection of posterior fossa tumour with an embedded qualitative study

8.1 Introduction

Physiotherapy is integral to the management of children with movement problems following surgical management of posterior fossa tumours (PFTs) (NICE 2005). Whilst there is a suggestion of benefit for acute inpatient rehabilitation for children with acquired brain injury (Bedell 2008) there is no evidence base to guide management of persistent ataxia in children with PFTs despite this being the most prevalent motor problem in this population group, as described in Chapter 2. It is known that ataxia can be a long-term problem for children with PFT with up to 70% of children presenting with persistent ataxia and balance problems (Hartley et al. 2018, Piscione et al. 2014), yet the literature review highlighted the lack of evidence to inform physiotherapy interventions in this area. It has now been demonstrated that recovery slows following the acute period (Phase 1), therefore it is of real importance to consider if physiotherapy intervention can assist in this population. Work has also established the potential of the SARA and BARS scales to assess change in ataxia in children and informed the decisions about the suitability of outcome measures (Phase 1) for children with PFT.

The clinical need for this research is also matched by the priorities raised by the PPI group consisting of families who had experience in this area. The systematic literature review presented in Chapter 3 noted that although the evidence was low level, there was a suggestion of benefit for physiotherapy for children with ataxia from different pathophysiological underpinnings. In particular there was a trend in the literature for using virtual training (VRT) as a modality/setting in children with ataxia which was supported by

physiotherapists across different countries in the e-survey (Phase 2). VRT interventions offer the opportunity of repeated practice of tasks thus using principles of motor learning and balance training as discussed in Chapter 7 and there is established support for the use of VRT as an intervention (Phase 3).

In summary, the previous phases of this study established a clear need for research to examine the use of VRT as a physiotherapy intervention to guide physiotherapists treating children with ataxia following surgical resection of PFT. All previous phases of this research programme informed the initial development and planning of this feasibility RCT intervention trial (Phase 4) for children with ataxia following surgical resection of PFT. The protocol of Phase 4 was refined using specific information provided by each phase of the study as follows:

- Phase 1 provided information regarding inclusion criteria, choice of outcome measures (including proposed MCID for ataxia scales)
- Phase 2 provided information regarding use of VRT in children with PFT and length of treatment sessions
- Phase 3 informed the choice of video games for the intervention group.

The CONSORT extension statement for reporting of pilot/feasibility studies (Eldridge et al. 2016) has been considered throughout this chapter.

This chapter presents Phase 4 data collected up until the end of February 2021.

8.2 Research question

The main research question for this (first of its kind) study was ‘what is the feasibility of conducting a randomised controlled trial to examine the effectiveness of virtual training in children with ataxia (usual care and virtual training versus usual care) following surgical resection of posterior fossa tumour’?

8.3 Aims

The aims of this study (Phase 4) were to:

1) Determine the feasibility of conducting a RCT examining the effectiveness of virtual training and usual care versus usual care on ataxia in children following surgical resection of posterior fossa tumour considering the:
    a) feasibility of RCT design; and the
    b) feasibility of virtual training intervention; and
2) explore children's/parent's perceptions of feasibility and acceptability of virtual training.

8.4 Specific objectives

The objectives of Phase 4 were to:

1) Examine the process measures (e.g. number of children identified and subsequently recruited, willingness to be randomised, number of children who complete all assessments);
2) examine the intervention measures for the hospital and home-based sessions (e.g. number who complete all intervention sessions, adherence of home training programme);
3) assess the appropriateness of the outcome measures (including any issues with completion of specific outcome measures, and ease of use in the clinical setting);
4) gain an understanding of the child's and parent's perceptions of virtual training and factors influencing acceptability, practicality and adherence to continuing the intervention at home; and
5) provide data to inform sample size estimate for a future definitive and fully powered trial (based on measures of recruitment rate, drop out, withdrawal, non-completion and group variability of outcome measures).

8.5 Study design

8.5.1 Feasibility study

A feasibility study was planned to build the foundation for future research in this area. Due to the lack of literature in this field it was important to start with a feasibility study to gain a greater understanding of the processes involved in setting up a study of this design examining virtual training in children with PFT. A feasibility study is defined by the National Institute for Health Research (NIHR) as:

'a piece of research done before a main study in order to answer the question 'can this research be done' … used to estimate important parameters that are needed to design the main study' (NIHR Glossary 2018).

Key questions with regard to Phase 4 were access to participants, recruitment rate, willingness to be randomized, completion rate of intervention and selection of outcome measures; these factors all fall under the remit of a feasibility study (Abott 2014, Morgan et al. 2015). At this stage the priority was to understand elements of recruitment, whether the protocol was acceptable and also feasibility of the intervention itself (as the intervention had not previously been described in this population), and whether it could be implemented. These elements are also characteristics of a feasibility study (Bowen et al. 2009). A feasibility RCT was best suited to answer these questions in terms of examining both feasibility of the RCT design and feasibility of the intervention.

8.5.2 RCT design

It can be particularly difficult to design and implement 'therapy' trials due to several factors. Firstly, a lack of literature relevant to therapy trials means it is difficult to develop and refine protocols; thus, preliminary work in the form of a feasibility study needs to be undertaken first. Additionally, in terms of therapy provision, 'routine' practice (i.e. usual care) often consists of a multimodal treatment approach, and intensity can vary across different settings

(e.g. acute or community locations) meaning a pragmatic approach is required (Tickle-Degnen 2013). Furthermore, in an acute paediatric population, there is also the challenge of considering the influence of age, growth and impact of medical interventions, e.g. adjuvant oncology management may influence physical presentation in this population.

When planning the study in the first instance different research designs were considered (e.g. single case experimental design (SCED), cross over trial, single arm feasibility study) to test the intervention. However, as RCTs are generally accepted as the gold standard method for evaluation of health care interventions (Tilling et al. 2005) this was the preferred design. RCT designs include the random allocation of participants into one of two (or more) groups aiming to reduce bias and increase internal validity as this adds strength to the quality of any results (Alford 2007).

In this study, implementing a feasibility RCT also allowed the impact of recruitment to an intervention and control group to be explored and to determine the acceptability of the randomization procedure which aimed to inform future larger RCT studies (Morgan et al. 2015).

The starting point for this study was to consider a physiotherapy intervention compared with usual care. As it was not deemed ethical to remove usual care from the intervention group, the design chosen was usual care versus intervention (virtual training) plus usual care. It was acknowledged that the trial design would be underpowered and therefore no inference regarding group difference could be made. However, in order to know if the design of the RCT was achievable it was important to test feasibility with a small model of the optimal design. This design (with 2 groups and continuation of any pre-existing therapy provision, deemed 'usual care') is similar to that used to explore the effects of video gaming in the adult stroke population (Sin & Lee 2003). Elements of the design that increase internal validity such as assessor blinding and allocation concealment (Schulz & Grimes 2002) were considered if they were compatible with a pragmatic approach.

8.5.3 Mixed methods approach

A mixed methods approach was chosen to best meet the aims of the study. This enabled the collection of both quantitative (e.g. process measures such as recruitment rate) and qualitative data (e.g. parent/child feedback) to develop a more complete understanding regarding feasibility outcomes of both the RCT design and virtual training intervention. An embedded design was used to enable nesting of qualitative data within the otherwise predominantly quantitative evaluation of the intervention (Creswell et al. 2011), to understand how the child participants and their parents perceived the intervention. This also facilitated examination of concurrent and retrospective acceptability of the intervention (Sekhon et al. 2017). It is acknowledged that mixed method approaches can place a higher burden on the participants in terms of time commitment and require increased resources (Hesse-Biber & Johnson 2015). However, in this case the additional information gathered from the participants was valuable to increase the breadth and depth of understanding of the feasibility measures (Irvine et al. 2020). The time burden for the participants was minimized as far as possible (discussed in section 8.11). Details of both quantitative and qualitative data analysis and merging of these analyses are discussed later in the chapter.

8.5.4 Protocol development

8.5.4.1 Intervention protocol

Informed by the literature previously discussed relating to children with ataxia, VRT - specifically the Xbox Kinect - was chosen as the intervention. The specific protocol regarding game choice was informed by the workshops conducted in Phase 3 of this study. Child, parent, and clinician feedback was used alongside the Kinect-ing With Clinicians (KWIC) framework to produce a comprehensive review of potential games (as previously presented in Chapter 7 and Appendix 31). This framework was then examined with the research team to produce a gaming matrix (Appendix 32) for the intervention therapists to follow. This generated a defined protocol to ensure replicability although there was built in capacity for progression and adaptation for age and compliance. This approach is similar

to that used in a study of exergame training for children with advanced degenerative ataxia (Schatton et al., 2017).

Dosage

The intervention 'dosage' (duration, frequency, intensity) was informed by the literature in this area (as presented in Chapter 3 and 7), and further refined with feedback from the PPI group involved with this study. Five families (as detailed in Chapter 4) were asked to consider elements of protocol design including length of sessions, overall number of visits to the hospital and intensity of the intervention.

The duration of intervention was initially guided by the literature. Although there was wide variation in studies, the median length of therapy interventions for children with ataxia was 7 weeks, and the median length of intervention for virtual rehabilitation training (VRT) in children with varying pathologies was 6 weeks. The PPI group felt attending hospital for a 4-week block of physiotherapy intervention was practical to complete, and it was also important to consider if the intervention could be continued at home. Therefore, it was decided that the protocol would include a 4-week initial intervention block attending the hospital followed by 4-weeks at home.

The intensity of intervention was also informed by the literature review (the median number of sessions per week reported was three for both literature on therapy interventions for children with ataxia and the use of virtual training for children with different conditions). The PPI group confirmed this would be the maximum numbers of times they thought would be feasible to attend the hospital per week, so the intervention was set at 3 times per week. The e-survey provided information regarding physiotherapy session length where the therapists typically used 45-60-minute sessions which was in keeping with the literature review for therapy interventions for children with ataxia where the median session length reported in the literature was 45 minutes. The literature review, PPI and e-survey demonstrated coherence and together informed the selection of frequency/length of

physiotherapy sessions. The adult Cochrane review by Laver et al. (2012) on virtual training and stroke also noted that the threshold for a significant effect (reported in upper limb function and activities of daily living) was over 15 hours of training. Therefore, it was also considered the protocol should aim to reach this threshold, with a significant proportion of these hours built into the protocol to be therapist supervised to ensure training was completed. With this in place, the additional home training in the second 4-week phase of the study aimed to reach and then potentially exceed this threshold to consolidate effects. This approach acknowledged literature reporting that adherence to home exercise programmes can be low (Maring et al. 2013) but can be improved with collaborative planning with the parent/child (Novak 2011). Novak et al. (2009) described the impact of a home exercise-based therapy programme for children with cerebral palsy, reporting that the programme was clinically effective if it was implemented 17.5 times per month for an average of 16.5 minutes per session. Further information regarding training thresholds for home exercise programmes would be valuable to guide therapy protocols in the future. Consideration was also given to the literature within the motor learning field which described the time required to learn a new balance task as 45 minutes, once a week for 6 weeks (i.e. 4.5 hours) (Taubert et al. 2010). However, it is not clear whether additional time is required for children with cerebellar pathology with known issues with motor learning. Overall, the intervention protocol was similar to that used by Ilg et al. (2009, 2012) with children and adults with ataxia from a genetic origin, thus providing confidence that the intervention protocol could be undertaken. Table 8.1 illustrates comparison of research design in similarly focused studies.

Table 8.1 Comparison of study protocols

Dose	Phase 4 study protocol	Ilg et al. 2012	Ilg et al. 2009	Schatton et al. 2017
Duration	4/52 hospital based 4/52 home based	2/52 clinic based 6/52 home based	4/52 clinic based 8/52 home based	Phase 1 1/52 clinic based 5/52 home based Phase 2 2/7 booster clinic 5/52 home based

Frequency	3 x week clinic 3 x week home	4 x week at clinic Varied frequency at home	3 x week clinic Daily at home	Phase 1 4x week clinic Phase 2 3x week home
Intensity	60 min session	60 min session at clinic 20-175 min per week at home	60 min at clinic 60 min at home	Phase 1 60 min session at clinic Phase 2 45 min session at home in second phase

Min = minutes

8.5.4.2 Assessment procedures

Assessment at three time points was built into the study protocol. Participants were randomized after the initial assessment to allow stratification according to age and severity of ataxia. This was important as age can influence physical presentation and the impact of ataxia severity on potential for improvement has not yet been determined and may be a prognostic factor. The initial baseline assessment included outcome measures as discussed below and also incorporated the inventory of non-ataxia signs assessments (INAS) to ensure ataxia was the primary presenting movement disorder. The INAS would identify signs of peripheral neuropathy as a result of chemotherapy and/or hemiplegia as these impairments may be present depending on the extent of the tumour and surgical resection. The second assessment was completed eight weeks after baseline for both groups. A third assessment was included to check for maintenance of potential change although, due to the time frame for the study, only a short-term follow-up was possible. In future studies it would be valuable to consider a longer term follow up assessment. This third assessment went some way to evaluate the willingness of families to attend for a follow up assessment.

8.5.4.3 Selection of outcome measures

The outcome measures for the feasibility study were informed by Phase 1 and took into consideration the World Health Organisation International Classification of Functioning, Disability and Health (ICF) to encompass body function, activity and participation domains (as discussed further in section 8.8.2). It was known that the SARA and BARS are very

quick to complete in this population group (average of 4 minutes and 3 minutes respectively) (Hartley et al. 2015). The combination of the SARA, BARS, PEDI-m and a subjective scale were used for the CARS study in a timely manner with no issues noted. When Phase 4 of the study commenced only interim analysis of the responsiveness of the scales was available, at this time both scales were indicating potential to demonstrate responsiveness, and as both scales were being used in other larger trials (e.g. NORPHO Cerebellar Mutism Syndrome Study) they were retained for Phase 4 of the study. Additional measures to those used in the CARS study were added to include a specific upper limb measure (9HPT) and a balance scale (Paediatric Balance Scale) to cover specific elements of ataxia i.e. upper limb coordination and balance respectively. Both are normative referenced for children. A quality of life measure was also used, the Peds QL Brain Tumour Module was chosen as an internationally recognized quality of life measure in paediatric oncology. As additional measures were added it was of interest to record the time to complete all assessments to ensure this was feasible to do for children for a variety of ages. From clinical experience and with information from the CARS study, the selected measures were expected to take approximately 60 minutes to complete which would be the typical length of a therapy session.

8.6 Recruitment

8.6.1 Inclusion criteria

Children and young people aged 4 to 18 years (inclusive) who demonstrated ataxia following surgical resection of PFT were eligible to enter this study. Four years of age was set as the lower limit for the study due to the capacity for younger children to complete both the selected outcome measures and undertake the intervention protocol. In clinical practice and in the CARS study it was possible to assess children from 4 years of age using similar outcome measures. Additionally, the SARA scale has normative reference ranges from the age of 4 years (Lawerman et al. 2017a). For this study ataxia was defined as SARA greater

than 2. This cut off value was informed by the data from the CARS study (from the cut off threshold value distinguishing no ataxia from mild ataxia). Participants were also required to be 12 months to 3 years following surgical intervention. This time frame was selected as it the covers the time when the children will typically have completed any adjunct oncology treatment and therefore more emphasis is dedicated to rehabilitation. At this time point they also have regular follow up clinic visits and were thus accessible to the research team. From Phase 1 of this study it was also noted that children did not typically significantly improve during this time point (with regards to ataxia or functional ability) therefore it was of real interest (but not a primary objective of the study) to see if an intervention could influence physical presentation when natural recovery might be slowing.

8.6.2 Exclusion criteria

Children who were medically unstable or undergoing adjunct treatment (e.g. radiotherapy or chemotherapy) were not eligible to participate. This was to ensure that the children were well enough to complete the assessments and potential intervention, and also to minimise any potential effects of adjuvant treatment on their presentation. Children under the age of 4 years were not considered due to the difficulty with completing standardised assessments that focus on ataxia in this age group as stated previously.

Due to the requirements of the intervention protocol, children who were not able to stand independently for less than one minute (or with a SARA gait item of over 4) were not eligible as this would inhibit capacity to complete the training session.

Presence of co-morbidities with the potential to affect the safety of training (e.g. congenital or acquired disorders causing high risk of falls or lack of comprehension of training tasks), or current musculoskeletal impairments (e.g. a non-union fracture or fracture currently healing limiting weight-bearing) were also considered reasons for exclusion.

8.6.3 Recruitment target/Sample size calculation

Formal sample size calculation was not required as this was a feasibility study. However, in line with recommendations for a feasibility study (Billingham et al. 2013) and the time scale available, the initial aim was to recruit 40-50 participants (20-25 participants in each group). This target number was informed by previous databases held regarding the number of children with PFT managed by the acute host NHS Trust. However, following subsequent participant identification (and excluding children under the age of 4 years and those who had relapsed), lower than expected numbers were identified, therefore this target was adjusted to 30 (15 participants per group). A total sample size of 30 was thought possible, this would have allowed the recruitment rate to be estimated with an accuracy of 13%, with an expected recruitment rate of 40-50% of eligible children (deemed achievable considering the CARS study recruitment of 92%). The feasibility study would also consider an estimate of the retention rate.

8.6.4 Participant identification

Potential participants were initially identified at two tertiary Children's Oncology Units through screening of pre-existing neuro-oncology databases (conducted by members of the research team involved with the children's care). This was subsequently amended to four Children's Oncology Units (with two further amendments from the Ethics Committee to facilitate this process, in January 2019 and June 2019 respectively). These additional two units were required to optimise recruitment due to delays in opening sites and a lower than expected number of children who were eligible to enter the trial. Participants were identified from July 2018 (at the host site, with interruptions for COVID-19 and shorter periods of identification for the other sites as highlighted in Figure 8.3). At the time of submission of the thesis, the study remains open due to the significant impact on recruitment resulting from study suspension during 2020 as a result of the COVID-19 pandemic (as discussed in 8.14.5). This chapter only presents Phase 4 data collected up until the end of February 2021.

Parents of children who were identified by their respective neuro oncology teams were sent information by post containing an introductory letter about the study (Appendix 33), and parent and child (age appropriate) information sheets (Appendices 34-38). These parents were then approached in clinic by a member of the research team (e.g. CI or PI) to see if they would like to discuss the study further and determine eligibility. Parents were also given the option to contact the research team (either to their own site or myself as CI) directly with an expression of interest if wished as it was acknowledged that some children might not have a scheduled hospital appointment soon after receiving the invitation letter.

8.6.5 Participant screening

A record was kept of all potential participants who were screened for eligibility and reasons for exclusion recorded as appropriate at each site. Potential participants who were screened but not eligible for the study due to time post-surgery, receiving adjunct oncology treatment or change in physical ability were eligible for rescreening later in the study period if the families wished to reconsider participation. Where appropriate, this was conducted at a subsequent clinic appointment.

Training on recruitment, screening and trial processes for staff at each site was completed by the CI at the initial site visit prior to any recruitment.

8.7 Trial processes

8.7.1 Summary of trial processes

Figure 8.1 illustrates a summary of trial processes.

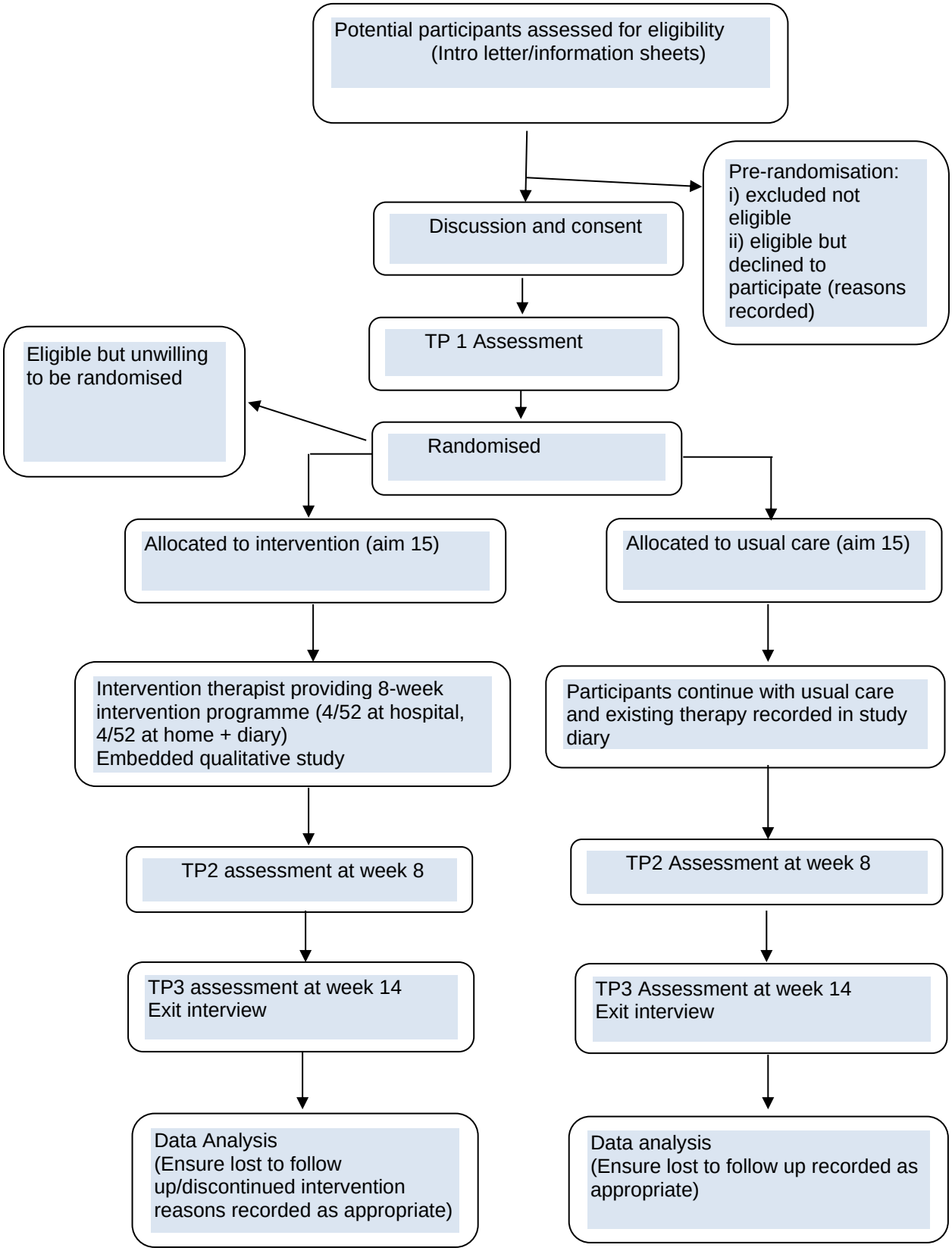


Figure 8.1 Trial Processes plan; flow diagram

8.7.2 Consent

Following screening, if the child met the inclusion criteria, a discussion took place with the CI/PI and child and their parent(s)/ person with parental responsibility regarding the study process. This included the nature of the study, objectives, randomisation process and time commitments. If the parents/child required any clarification regarding information in the parent and child information sheets this was provided (according to child's age/cognitive ability) and it was made clear that there was the opportunity to ask questions at any time. This allowed the researcher to confirm that the child and their family understood the requirements of the study.

If the child and their parents agreed to take part in the study informed consent/assent was documented using the appropriate consent and assent forms (Appendices 39-42); signed assent was gained, where applicable, dependent upon the child's age. The informed consent process was undertaken by members of the research team who were competent in this process and had undergone Good Clinical Practice (GCP) training with oversight from each site's principal investigator. If children did not want to take part at this point their reasons for not participating were documented if the families wished to share this information.

8.7.3 Randomisation/allocation

After obtaining informed consent and following assessment 1, children were randomised into one of two groups: current provision (usual physiotherapy input) vs virtual training plus continuing usual physiotherapy input. Block randomisation, informed by the initial CARS study, was used to ensure balance between the two groups; this was stratified according to age (4-10 years and 11-18 years) and severity of ataxia (2.5-5.5 and >5.5). Two age strata and ataxia severity groups were considered for block randomisation due to the small sample in this study. Information from the CARS study showed that the majority of children present with mild ataxia; therefore, children categorised as mild ataxia according to SARA score

were in one strata and children with moderate or severe ataxia were within the other strata. This aimed to facilitate a large enough sample for both intervention and usual care groups.

Randomisation was undertaken using sealedenvelope.com, a recognised online randomisation database for clinical trials recommended by the study statistician. This ensured allocation concealment.

8.7.4 Blinding

The assessor therapist was blinded to which group the participant was allocated to throughout the child's participation in the study. Children and their parents were asked not to disclose details of group allocation to the assessor. The assessors were asked at the end of the study about blinding and asked whether any allocation had been revealed to them, this aimed to provide information about study processes. The Chief Investigator (CI) was unblinded after the participant had completed all the assessments; this was done to facilitate the exit interviews which were performed by the CI.

8.7.5 Baseline data

Initial baseline data regarding age, age at diagnosis, diagnosis, tumour location/histology, specific oncology treatment, co-morbidities, and current therapy input was recorded by the CI/PI for the relevant site; this was informed by parent feedback and supplemented by medical records (Appendix 43). The participants' community therapists were notified of participation in the study (with agreement of the child/family), and assessment results were shared following the child's completion of the study if the parents and community therapists requested this information.

8.7.6 Study assessments

Children were assessed at the following time points (see Table 8.2).

Table 8.2 – Assessment schedule

Time Point (TP)	Intervention Group	Usual Care
TP1	At time of recruitment (Immediately before intervention)	At time of recruitment
TP2	Post intervention (8 weeks post TP1)	8 weeks post TP1
TP3	6 weeks post intervention (6 weeks post TP2)	6 weeks post TP2

The PEDI, PedsQL and subjective outcome measure were completed by parental report to reduce the burden of clinical assessment time on the child within the session and to limit any unnecessary causes of fatigue. The SARA, BARS, PBS, INAS and PEDI measures were assessed adhering to the SARA, BARS, 9HPT, PBS and INAS instructions and PEDI manual, following a standardised protocol to ensure the same instructions were given to all children (Appendix 44). Further information regarding outcome measures is detailed in section 8.8. The time taken to complete these measures was recorded as a process measure. Order of assessment was determined by clinical judgement (e.g. to adapt for any issues such as fatigue thus representing normal clinical practice).

Assessment was carried out by a blinded research assessor. Assessors were experienced clinicians (defined as over 5 years specialising in paediatric neurophysiotherapy) and familiar with the outcome measures. One joint training session was provided prior to the commencement of assessments with the assessor therapists to optimise consensus in scoring and to confirm the rater protocol.

Assessors were asked not to discuss assessment results (with other assessors or intervention therapists), and data collection sheets were handed immediately to the research administrator to allow input of individual outcome measures onto the Case Report Form (CRF) and for storing after each assessment. This maintained assessor blinding.

The option of remote video assessments was introduced in response to the COVID-19 pandemic via a research ethics committee amendment (submitted May 2020). Any challenges to completing outcome measures by remote assessment were recorded.

8.7.7 Intervention group (Virtual training plus usual care)

The first half of the intervention was carried out at the child's lead tertiary oncology centre overseen by the intervention therapist and consisted of a 4-week therapy block of Kinect 'virtual training'. Participants were offered 3, one-hour sessions per week over this 4-week period. Appointments were provided as flexibly as possible to minimise time out of school, if requested by parents.

The gaming matrix developed following Phase 3 was used to guide the intervention therapists to deliver the virtual training (discussed in Chapter 7 and presented in Appendix 32). Intervention therapists recorded the virtual training completed in the sessions in an intervention log (Appendix 45). A manual handling risk assessment for each participant was carried out prior to the start of intervention (according to Association of Paediatric Chartered Physiotherapists (APCP) guidelines) to minimise any potential issues regarding safety e.g. risk of falls. A postcard (Appendix 46) was sent 2 weeks into the study by the research administrator, to remind the participants to fill in their study diary.

The child and their parents were then asked to continue their training programme at home for a further 4 weeks (equipment was provided if they did not have it already available in their home). They were given a written training plan (issued by the intervention therapist and agreed by the child/parent) as a memory aid and to aid fidelity (Appendix 47). A home-based risk assessment was undertaken through therapist and parental discussion.

A follow-up phone call was carried out by the intervention therapist one week into the home training period to check for any problems/queries with the home-based training programme. This call also reminded the families to complete their study diaries in order to evaluate

compliance (see Section 8.7.9 for further details). The child and their parents were offered a follow up appointment at their participating site 1-2 weeks into their home exercise programme as an opportunity to progress training or review any problems, as appropriate.

Children and their families were asked to document the intensity of playing the games at home in their study diary (including frequency and duration of sessions) (Appendix 48). Any existing physiotherapy input (usually community based or a home exercise programme) continued during this intervention period. The type of intervention and frequency/duration of their existing physiotherapy were recorded in their study diary. A phone call was carried out at 7 weeks into their participation by the research administrator to remind the participants to bring their study diary and return their virtual training equipment at their follow up assessment.

The option of remote video virtual intervention sessions was introduced as a response to the COVID-19 pandemic via a research ethics committee amendment (November 2020). There was still the requirement to complete a minimum of two sessions on site to enable a risk assessment to be completed and to establish that the child and their parent could safely take the equipment home and begin training. Following the first two sessions on site, any further sessions that previously would have been conducted at the hospital site were available supervised at home (via the attend anywhere platform), dependent upon parent and child choice and the practicality of the child attending on site. The second unsupervised block of home training remained as per the original protocol.

8.7.8 Control group

The control group undertook their usual care (i.e. physiotherapy input in the community or previously instructed home exercise programme). It is acknowledged that this may be different across the community settings, therefore any physiotherapy undertaken in the study period was logged by the participants in their study diary. The type of intervention and

frequency/duration were recorded. Assessment of risk for usual care was undertaken by the usual care (i.e. community) therapy teams, where relevant.

A postcard was sent two weeks into their participation, by the research administrator, to remind the participants to fill in their study diary (Appendix 46). A follow up phone call was undertaken at 5 weeks and 7 weeks (to ensure the reminders are the same for both groups) to check if there were any issues and remind the participants to fill in their study diaries and to return these at their follow up assessment.

8.7.9 Participant diaries

A study diary was also used to evaluate compliance (Appendix 48). All children who participated in the study were given paper diaries to log both trial and non-trial related physical activities during the study period. Physical activity was defined as structured activity e.g. sporting activities/PE. All the children/their parents were also asked to record the amount of time spent on video gaming activities in addition to those undertaken as part of the study.

8.8 Outcome measures

8.8.1 Measures related to feasibility

Measures related to feasibility are presented as process measures and intervention measures. The process measures will inform the stop/go criteria regarding the undertaking of a full trial in the future. Criteria were set around recruitment rate (aim 50%), percentage drop out and outcome measures.

Reporting of terminology of outcome measures for a feasibility/pilot study is unclear. Often the terms ‘primary and secondary outcome measures’ are not used in feasibility/pilot trials as this terminology is typically associated with a full trial. Indeed, a feasibility study often aims to determine what the primary outcome measure should be. However, the option of using ‘primary/secondary outcome measures’ is included in the CONSORT 2010 guidance

extension for pilot and feasibility studies (Eldridge et al. 2016). The CONSORT extension text makes it clear that outcomes can be measurement or assessment if they meet the pre-determined objectives (Eldridge et al. 2016). Thus, for this feasibility study 'measures of feasibility' have been used.

The process measures of feasibility were:

1) The number of participants identified who met the inclusion criteria and were then subsequently recruited;
2) Reasons for not participating were also noted alongside willingness for randomisation; and
3) The number of participants who completed all assessments were recorded along with the time required to undertake the assessments and any missing items.

The assessment measures of feasibility were:

1) The number of missing items/non-completion of any outcome measure; and
2) Any issues with completion of outcome measures were recorded.

The intervention process measures of feasibility were:

1) The number of participants who completed all sessions of the intervention and the child's adherence to treatment in the home setting;
2) Any barriers to delivery of the treatment in the clinical setting and home setting were also documented; and
3) Recording of any adverse events.

8.8.2 Outcome measure analysis (Related to effectiveness of Intervention)

The outcome measures were selected on the basis of the ICF (International Classification of Functioning, Disability and Health) to cover the spectrum of body function/structure,

activity, and participation domains. Whilst the impact of the intervention was not the focus of the feasibility study, it was acknowledged that preliminary analysis could offer confidence in the intervention and inform the sample size for a future definitive trial. Determining which outcome measure would be the primary outcome measure for a future trial could also be examined if possible (dependent upon number of children recruited).

The measures selected are detailed in the following Table 8.3 (Note: where measures are not subject to copyright, they are also included in the Appendices).

Table 8.3: Outcome measures (related to effectiveness)

Name of measure	Focus/aim	Completed by	No of items	Score (range)	Comments	ICF
SARA (Scale for the Assessment and Rating of Ataxia). (Schmitz-Hubsch et al. 2006) Appendix 1	Rate severity of ataxia.	Clinician.	8	0-40 (40 represents severe ataxia).	Reliable and valid in children with PFT. Normative values available (Lawerman et al. 2017a).	Body function and structure.
BARS (Brief Ataxia Rating Scale). (Schmahmann et al. 2009) Appendix 2	Rate severity of ataxia.	Clinician.	5	0-30 (30 represents severe ataxia).	Reliable and valid in children with PFT.	Body function and structure.
9 HPT (Nine-hole peg test). (Mathiowetz et al. 1985)	Measure of upper limb function.	Clinician.	2 trials each for dominant and non-dominant arm.	N/A – timed.	Normative referenced in children and adults (Smith et al. 2000).	Body function and structure.
PEDI (Paediatric Evaluation of Disability Index) PEDI-m (mobility domain) PEDI-sc (self-care domain). (Haley et al. 1992)	Impact on function and activities of daily life.	Clinician or parent (questionnaire).	Mobility domain 59. Self-care domain 73.	Raw score mobility 0-59 (59 no problems). Self-care 0-73 (73 no problems). Scaled score 0-100 (100 represents no problems).	Normative referenced from 6 months to 7.5 years. Can be used in older children if skills fall below expected level (Hayley et al. 1992). MCID 11 points (Iyer et al. 2003).	Activity and participation.
Peds QL Brain Tumour Module.	Impact on quality of life.	Parent and child (self-report).	Dependent on child age.	Each item scored out of 4 (4	Validated in children with	Participation.

(Varni et al. 1998)			Domains include worry, procedural anxiety, physical and cognitive difficulties.	representing more problems).	brain tumours (Palmer 2007).	
Paediatric Balance Scale. (Franjoine et al. 2003)	Impact on balance.	Clinician.	14	0-56 (56 represents no problems).	Reliable in children with moderate impairments. Normative referenced from 2-13 years (Franjoine et al. 2003, 2010). MCID reported in CP (3.66-5.83) (Chen et al. 2013).	Activity.
INAS (Inventory of Non-Ataxia Signs). (Jacobi et al. 2013)	Allows the determination of non-ataxia signs e.g. peripheral neuropathy, hemiplegia.	Clinician.			Reliability determined but poor responsiveness shown (Jacobi et al. 2013).	Body function and structure. (used as screening tool only on the first assessment)
Subjective impact (Appendix 49)	Subjective report of any improvement (or deterioration in ataxia).	Parent/child (self-report).	Single scale.	-2 (ataxia much worse) to +2 (ataxia much better).	Likert scales regularly used in research.	N/A.

8.9 Embedded qualitative study

8.9.1 Sample

Due to the lower revised recruitment target (discussed in 8.6.3) all children and their parents in the intervention group were asked if they would like to take part in the embedded qualitative study. This study aimed to capture the views of children and their parent(s) from the intervention group with different severities of ataxia and tumour histology.

Children/parents were recruited at the time of entering the study for this component, with written information detailing this element of the study in the PIS. The minimum sample size aim for this part of the study was 50% of the intervention group (n=7).

8.9.2 Procedures

The child's parent(s) were invited to take part in a short focused, semi-structured interview (approximately 5-10 minutes in the therapy department) at the start of the intervention (end of week 1) and at the end of the 4 weeks of hospital based sessions with the chief investigator/intervention therapist to allow exploration of a particular topic (e.g. acceptability of the intervention or barriers to attending for the specified protocol) (Appendix 50).These topics were selected to help inform the specific objectives of Phase 4, aiming to add insight to the measures of feasibility and the quantitative data. This element of data collection was kept short to reduce the time burden on the parents. With the parent's permission the interview was audio-recorded.

Dependent on the preference (and age/cognitive ability) of the child, the child was asked if they would like to provide feedback to the same questions. Alternatively, an option to complete a short child friendly version of these questions was also used (on a study tablet via Survey Monkey using pictorial feedback e.g. smiley faces, Figure 8.2).

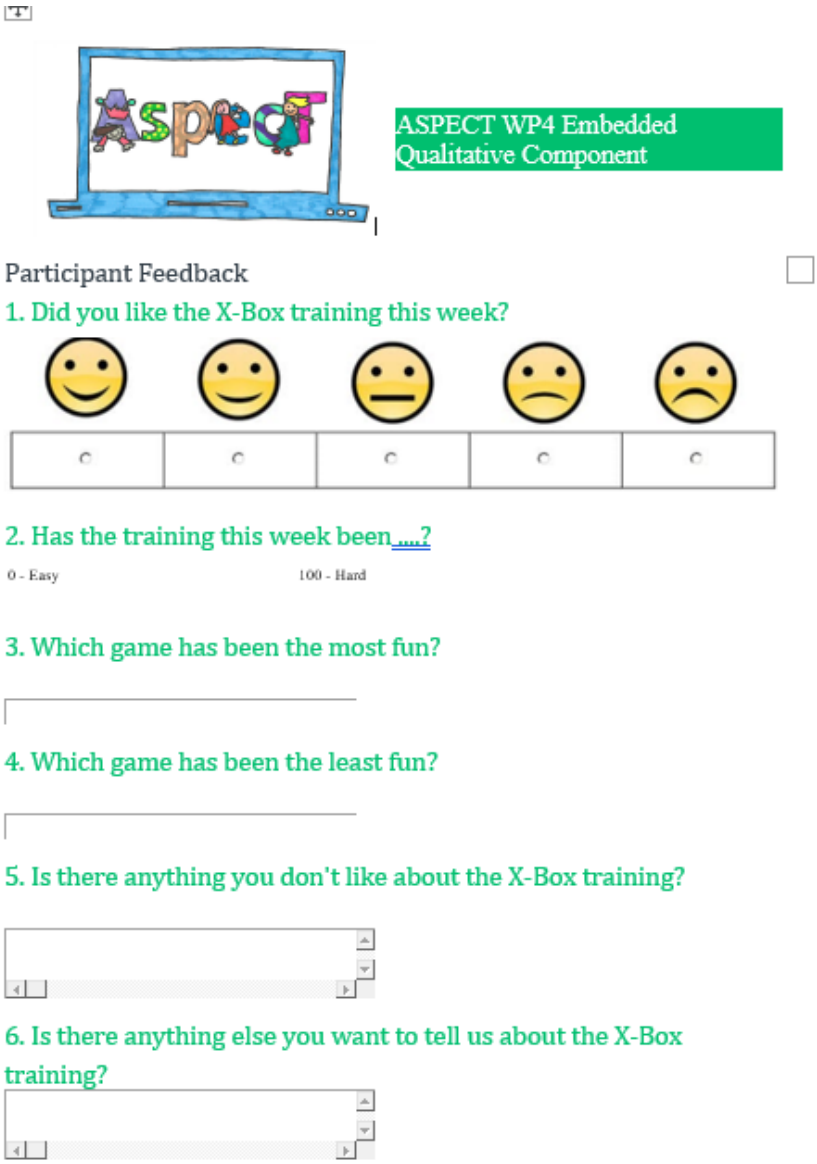


Figure 8.2 Child Friendly intervention interview

A remote exit interview (Skype/telephone) with the parent most involved with supporting the intervention at home was completed by the lead investigator within 2 weeks of the final assessment to explore the parent's experience of undertaking the intervention. Although generic guidance (e.g. opening script, potential questions) had been prepared (Appendix 51), each exit interview was informed by a preliminary analysis of the diary and interview data relevant to the specific family. With the parent's permission the interview was audio recorded. Children and young people who wished to contribute their ideas about home-based training, were invited to talk to the researcher with their parent over Skype/telephone.

Families who did not complete all of the intervention but participated in the qualitative study were still asked to participate in the exit interview within 2 weeks of withdrawal. Particular areas that were explored were the acceptability and practicality of the intervention, any barriers to completion, expectation of the study and perception of the effectiveness of the intervention.

Interviews conducted both during the RCT (i.e. week 1 and 4) along with the exit interview allowed the examination of concurrent (whilst participating) and retrospective (after the intervention) acceptability (Sekhon et al. 2017).

8.9.3 Exit interview control group

Parents of children who were in the control group were also asked if they agreed to a short exit interview over the telephone/Skype at the end of their child's participation in the study. This was a structured interview to collect information specific to willingness for randomisation, drop out, potential non-completion, and feasibility of assessment. This was completed by the CI after the point of unblinding, i.e. when the child had completed all three assessments (Appendix 51).

8.10 Ethical issues

Phase 4 of the study was submitted with Phase 3 as a joint ethics application, as detailed in section 7.9 (IRAS ID 227917, Appendices 16 and 17 for REC and HRA approval). Ethical considerations regarding gaining informed assent or consent from children of different ages (and potentially differing cognitive ability), and the time/travel burden of the children and their parents were considered throughout the design and conduct of the study.

Four versions of participant information sheets (PIS) (4-6-year-old version, 7-10-year-old version, 11-15-year-old version and 16-18-year-old version) were prepared for children of different ages/cognitive ability to enable them to gain as much information as possible about the study (Appendices 34-38). The version for younger children (4-6-year-old) included

more pictorial information than the other age-group sheets and used very clear basic language. A parent information sheet was also produced, and this included information about potential involvement of parents in the embedded qualitative component. The information sheets clearly explained the randomisation process and time commitments of the study. The PIS sheets were developed with advice from the steering group which included parent representation and utilising NIHR guidance materials (hra-decisionstools.org.uk). Assent forms were used, where appropriate, alongside parent (or young person) consent forms where applicable (Appendices 39-42). The chief investigator and PIs for all sites had completed GCP training within the past two years of them recruiting for this study.

In order to promote inclusivity, time and financial burdens were minimised as far as possible. There was incorporation of quick to use outcome measures (e.g. it was previously demonstrated in the original CARS study that the SARA and BARS each can be completed in under five minutes). Flexible appointments were offered to coincide with clinic visits/pre-existing trips to the hospital, where able, or in school holidays, if preferred. Home based delivery with provision of equipment, as part of the intervention was also integral to the research design. Reasonable travel expenses were available for visits to the hospital specifically for the purpose of the study. In addition, the exit interview was completed by telephone/Skype to reduce visits to the hospital.

Although the virtual training intervention was not anticipated to cause any problems for the participants, individual risk assessments were completed by the intervention therapists before beginning the intervention (in order to reflect the child's physical capability and any co-existing morbidities that may affect training alongside consideration of the environment).

8.11 Research governance

8.11.1 Data protection and confidentiality

Data protection and confidentiality issues were considered throughout the design process and during the implementation of the study. On entering the study, the participants were allocated an identification number and subsequently all data were pseudoanonymised. Personal data were only accessed by individuals within the direct care team and available only via password protected NHS computers. Participant information sheets also included information for participants and their parents on how their data may be handled and shared. Following the implementation of GDPR (2018) an additional data information sheet was also provided to the participants (amendment 1, Appendix 27). A data management plan was created (Appendix 52).

8.11.2 Data handling and record keeping

Management and transfer of data were also considered. The initial data were inputted by the research administrator and, then at the point of unblinding, were transferred to the CI (through a secure network). The data were stored electronically on a secure password protected network. The CI with the support of the statistician were responsible for data analysis. Audio recorded qualitative data were transcribed by the researcher and kept on a secure network with password protection. The interview transcripts were anonymised (using pseudonyms assigned by CI). The audio data were deleted following the completion of transcription. All electronic data were stored as above on a password protected secure network. All paper-based documents were stored in a locked cabinet within a pass protected room in line with the data management plan (Appendix 52).

8.11.3 Data archiving

In line with the host NHS Trust guidelines all essential documents will be archived for 10 years after completion of the study. Destruction of essential documents will require authorisation from the sponsor. Parent information sheets (PIS) informed the participants and parents regarding data storage.

8.11.4 Reporting

Phase 4 (and Phase 3 of the study) were subject to REC, HRA and NIHR reporting. The study was overseen by the immediate supervisory team, and steering group committee (consisting of internal and external members and a parent representative). Procedures were in place to report any adverse event that may have occurred during the feasibility RCT to the appropriate REC committee as required as specified in the protocol.

8.12 Data Analysis

8.12.1 Analysis of measures related to feasibility

Feasibility processes were reported descriptively and included how many children were identified and how many of those were recruited. (Corresponding confidence intervals were planned to be reported when appropriate, but this was not possible due to the small numbers of children in the intervention group). Any issues with recruitment or reasons for refusal to participate were reported. Any participants who did not complete the full intervention or missed any follow up assessments were documented. This was presented in a CONSORT flow diagram.

8.12.2 Summary of baseline data

Baseline data for all recruited participants were reported in table format and a comparison between the two groups was presented descriptively. Data included age, age at diagnosis, diagnosis, tumour location/histology, specific oncology treatment (e.g. surgical management, adjuvant chemotherapy or radiotherapy), co-morbidities and current therapy input.

8.12.3 Outcome measure analysis (related to effectiveness of intervention)

Owing to the nature of this study being a feasibility pilot and not a fully powered RCT, the initial plan was to adopt non-parametric statistics and report any significant differences as ‘trends towards significance’. However, in view of lower numbers recruited and an uneven

split between the intervention and usual care arm, individual results are presented graphically to illustrate change for each outcome measure across assessment time points. The intention was to use the outcome measures (in particular the SARA) to inform a sample size calculation for a future definitive RCT. For the purpose of communicating the intended method, an example of this is reported in this thesis. However, since the trial is ongoing this calculation will be repeated when the study is fully completed with a larger number of participants.

8.12.4 Embedded qualitative study data analysis

All field notes and audio-recordings were transcribed verbatim. A thematic analysis (Braun and Clarke 2006a & b) of the data was undertaken by the chief investigator. An initial reading of the transcripts identified broad codes which summarised similar sections of data. The codes were then refined and re-organised through an iterative process which included re-reading and re-working the analysis, moving between transcripts and codes. Convergent and divergent perspectives were included in the analysis. Preliminary themes were then inferred from the data. Initially, each parent's data and each child's data were analysed separately before being considered as part of a family 'case'. Then all parental data and child data were considered as separate data sets. The themes were then reviewed, and the final set of themes were named. An analysis of each theme was written up using a narrative description and data extracts.

8.12.5 Integration/merging procedures

The quantitative data from the process and intervention measures were reported together with the qualitative data gained from children and their families. Side by side displays of the quantitative and qualitative data are presented and structured according to the aims of the study (Creswell 2015, Warland et al. 2019). These displays help to understand how the quantitative and qualitative data interact and provide new insights. The data gathered from the embedded qualitative study were fed into the analysis of the RCT results, providing

useful context and themes that supported understanding the process measure results and assessment of compliance. The qualitative data enabled the process measures to be explained in further detail.

8.12.6 Overall assessment of feasibility

Although the study is ongoing and any final feasibility recommendations will be made at the study close, a preliminary assessment of feasibility was made in relation to the set stop/go criteria.

8.13 Results

The results are presented considering principles of the CONSORT statement for reporting of RCTs (Schulz et al. 2010), and extension statement for feasibility/pilot studies (Eldridge et al. 2016).

8.13.1 Feasibility measures analysis

One hundred and forty-three children were identified across all 4 sites; all had been diagnosed with a PFT. Following screening (for age range, SARA score and time post-surgery) 41 children met the inclusion criteria as illustrated in the CONSORT Flow Chart (Figure 8.3). Seventeen children/parents expressed an interest in the study, and subsequently 10 children were recruited. Absolute recruitment numbers for each site (expressed as n=x) and the percentage recruited from those who were eligible at each site (expressed as %) were as follows: Site 1 n=8 (40%); Site 2 n=1 (6%); Site 3 n=1 (25%); and Site 4 n=0 (0%). Following identification of potential participants, Site 4 was unable to proceed with approaching children and parents and recruitment due to capacity of the local therapy service, secondary to COVID-19.

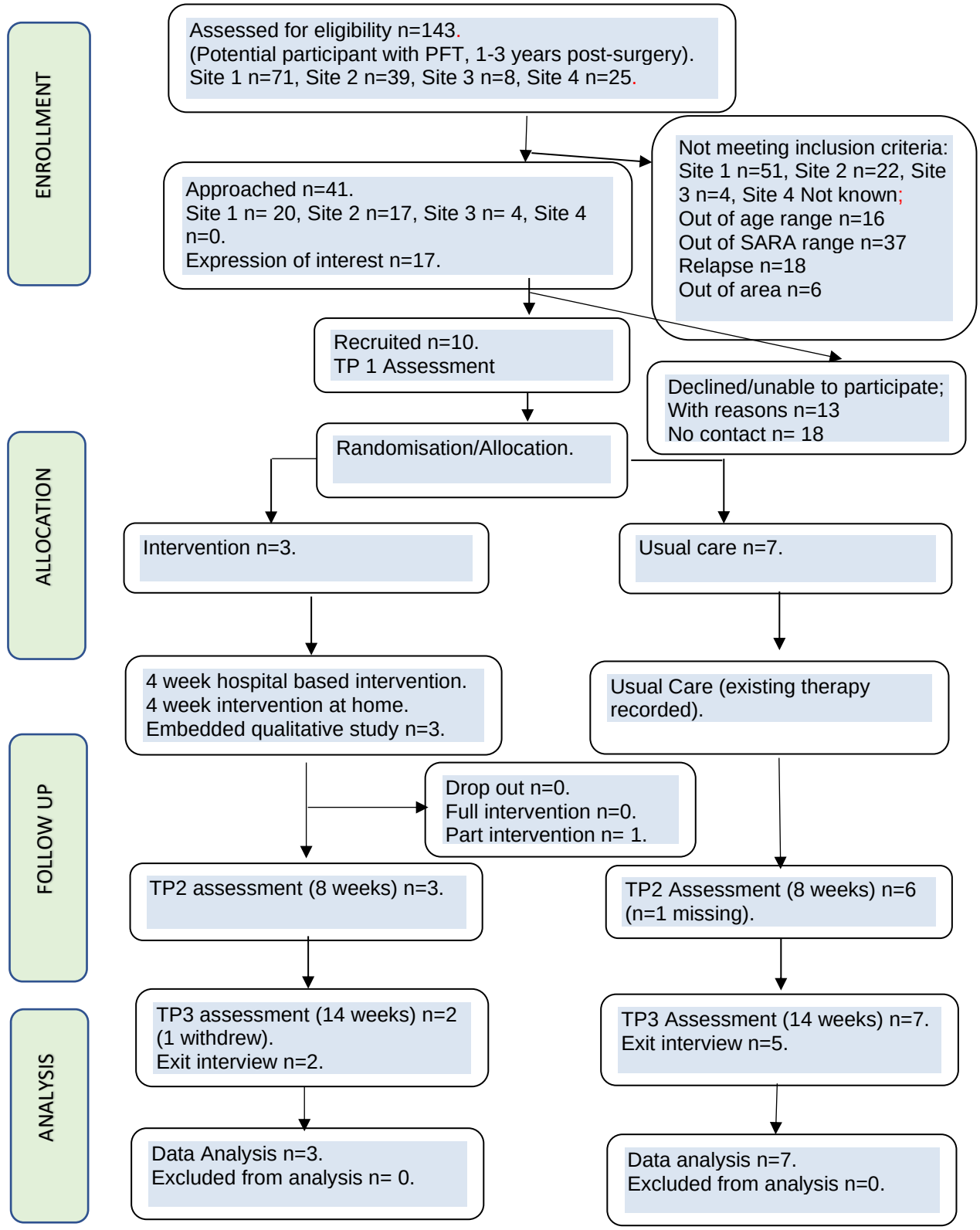


Figure 8.3 CONSORT Diagram

*Site 1: opened July 2018, suspended due to COVID on 19 March 2020, reopened August 2020
Site 2: opened January 2019, suspended due to COVID on 19 March 2020
Site 3: opened October 2019, suspended due to COVID on19 March 2020
Site 4: not able to open pre COVID-19 due to local delays, opened September 2020

Feasibility Process Measures

Reasons for not participating (where given) were a) family centred and included time and travel commitments required for the potential assessments/intervention, and the parent's perceptions of their child's anxiety regarding attending hospital, and b) study centred where disease relapse occurred whilst the child and their parents were considering participation (thus became ineligible). Field work notes were recorded during the study period to note any reasons for not participating and an example of these are illustrated below in Table 8.4.

Table 8.4 Fieldwork notes – reasons for not participating

Site	Reasons for not participating	Number
1	*Expression of interest but subsequently did not participate*	
	Due to visual impairment felt wouldn't be able to undertake intervention.	1
	Interested but did not proceed due to time commitment for intervention arm.	1
	Declined with reasons given	
	Too far to travel for assessments/intervention.	2
	Prefer to complete own activities in local area.	2
2	*Expression of interest but subsequently did not participate*	
	Interested but concerned re time out of school/parental ability to make number of Appointments needed for intervention therefore did not proceed.	2
	Planned to participate but unable to proceed secondary to increased anxiety with hospital visits.	1
	Relapse whilst considering participating.	1
	Declined with reasons given	
	Already completed similar virtual training treatment via brain injury charity and now wanted to focus on schooling and not physiotherapy.	1
	Too far to travel.	2
3	No further contact from participants sent information via post, therefore unable to determine reason for non-participation	N/A
4	N/A. Participants identified but unable to approach due to therapy redeployment secondary to COVID-19	N/A

A screening and recruitment log was also submitted monthly to the host site Research and Development Department to illustrate progress with screening/recruitment, and to identify themes for exclusion or declining participation. An example of this is detailed in Appendix 53. Due to concerns regarding slow recruitment, a recruitment graph was also used to track recruitment rate (as illustrated in Appendix 54), which illustrated target recruitment rate per

month, and provided an increased understanding of recruitment rate at different sites, highlighting when site contact was required. All participants (n=10) were willing to be randomised following recruitment.

One participant in the intervention group withdrew after the second assessment due increased medical appointments that were not study related.

Assessment/outcome measures

Overall, 10 participants who were recruited completed their assessment 1 (TP1), 9 completed assessment 2, and 9 completed assessment 3, meaning 80% completed all 3 assessment time points. The median time for assessments was 70 minutes. Assessment 1 was longer than assessment 2 and 3 due to time for discussion, consent process (if not already completed prior) and the INAS assessment. The INAS assessment was completed in all 10 participants.

Participants who were active in the study during the first wave COVID-19 completed partial assessments over the phone prior to the study suspension (the PedsQL, PEDI and subjective impact were only able to be completed via parental questionnaire). Following reopening of the study a further two participants were recruited and were offered remote video or face to face appointments. Families typically requested face to face appointments when given the option, with five out of six assessment appointments for the two participants conducted face to face (that is, only one remote video appointment was completed). During remote video assessments the 9HPT and BARS were not able to be completed due to equipment required or inability to assess eye movements via video appointment.

Twenty-four face to face assessments were completed. All outcome measures were completed for 15 assessments. The PedsQL child version was missing/not completed for six assessments. Reasons for non-completion of the PedsQL (where recorded) included ‘child’s attention’ and ‘understanding of the questions’. The PedsQL parent version was missing/not completed for 2 assessments. The 9HPT was not completed for the dominant

side on 1 occasion, and on 3 occasions on the non-dominant side. The BARS was not completed on one occasion, and the SARA was incomplete (although Bal-SARA completed) for one assessment due to difficulty testing limb items for one participant. Where the 9HPT, BARS and SARA were missing or incomplete this was all for the same participant who was the youngest child recruited at the age of 4, where attention difficulties were reported.

Concerns were raised by the assessor on site 1 regarding language used for one question of the Peds QL on the child version. This was regarding a specific question in the 'worry section', which was phrased as 'I worry that my cancer will come back or relapse' (8-12 and 13-18 year old versions) and as 'Do you worry that your cancer illness will come back' (5-7 year old version). This was due to some families reporting that they had not used the word cancer with their child. Therefore, following discussion with the families entered in the study at that time, the research team and assessors at the other sites, it was decided to check with the accompanying parent first what phrasing they would prefer to use e.g. tumour, or lesion or lump, or if the parent did not want the child to be asked this question this was omitted. The rater protocol was updated accordingly.

Intervention measures – hospital based

Three participants were randomised to the intervention group. No participants completed all of the hospital-based intervention sessions, 3 participants completed part of the hospital-based intervention sessions (median number of sessions completed n=7, out of a planned 12 sessions). Barriers to undertaking the intervention in the clinical setting were recorded and are illustrated in Table 8.5.

Table 8.5 Fieldwork notes – barriers to undertaking the treatment in the clinical setting

Site	Barriers to intervention in clinical setting	Number
1	Due to upper limb ataxia sometimes difficult to use arm to select and start games. Not able to attend x3 a week due to parent work commitments.	1 1
2	Fatigue when trying to attend x3 a week.	1
3	Fatigue with combined effect of travel and intervention.	1
4	N/A. Participants identified but unable to approach due to therapy redeployment secondary to COVID-19	

Intervention measures – home based

Barriers to undertaking the intervention in the home setting were explored in the participant/parent interviews and are presented later in the chapter.

Adherence to the home training programme for children in the intervention group was reviewed using the participant diary and also further explored in the participant interviews. One participant in the intervention group completed and returned their participant diary. Although each participant had a training plan recommending 3 sessions per week, participants reported via the participant diary and exit interviews that they had completed the training at home 1-3 times a week (median 2 sessions).

One non serious adverse event was reported when one participant reported significant fatigue during the study period which also coincided with other external commitments (centred around family travel). However, they were able to continue in the study.

Feasibility log

A feasibility researcher log was kept recording any overall feasibility issues throughout the study and this is presented in Table 8.6 below.

Table 8.6 Feasibility log

Area of feasibility	Sites involved	Specific Details
Recruitment: Identification/approach	All	• Lower number of potential participants identified than anticipated (based on previous PFT database held from 2009-2014). • Not costed for time/equipment required for set up of additional sites. • Impact of COVID-19.

		• Delays in opening other sites.
Recruitment: screening	Site 2	• Lower recruitment at site where neuro oncology clinics held off site (at different NHS trust).
Recruitment: consent	Sites 2-4	• Unable to directly arrange travel for potential participants who have no mode of own travel for all sites (except main sponsor site).
Protocol	All	• Not achieving full 12 sessions of intervention, median intensity 7 sessions.
Protocol	Sites 1 & 2	• Assessors reported became unblinded to participant group allocation for 3 participants.
Intervention	All	• Technology obsolete, Xbox no longer making Kinect. • Impact of COVID-19 on visits to site.
Outcome Measures	Site 1	• Concern raised by assessor therapists regarding use of language in PedsQl questionnaire.

8.13.2 Summary of baseline data

Ten children aged between 4 to 14 years of age were recruited into the study. The median time from surgery was 2 years. Six children were diagnosed with a medulloblastoma, two children were diagnosed with a low-grade glioma. At the time of recruitment to the study 50% were receiving physiotherapy input from their local physiotherapy team. Usual care continued as deemed appropriate by the local team during the study (although in some cases this was influenced by COVID-19). This ranged from weekly input to 3 monthly reviews. Participant characteristics are detailed in Table 8.7.

Table 8.7 Participant characteristics

Characteristic	Intervention	Usual Care
Gender Male Female	 2 1	 5 2
Age in years, at time of recruitment Median (range)	10, (5-14)	8, (4-14)
Years post diagnosis (1 to 3 years) Median	2	1
Histology Low grade glioma Medulloblastoma	 1 2	 1 4

Ependymoma Other	0 0	1 1
Currently receiving physiotherapy Yes No If yes, frequency range	 2 1 Weekly	 3 4 Fortnightly- 3-month review
INAS Count Median (Range)	 2, (1-2) (vision/cognition)	 0, (0-2) (vision/cognition/urinary)
Baseline SARA Median, (range)	 4 (3.5-10.5)	 6, (3.5-15)
Baseline Bal-SARA Median, (range)	 3, (2-6)	 2, (2-4)
Baseline PEDI-m (raw score) Median, (range)	 50 (37-59)	 54, (51-59)

8.13.3 Outcome measures analysis

Results of individual outcome measures for each participant are presented graphically below. To demonstrate as much information as possible all participants results are included even if they only completed two assessment time points. Participants in the intervention group (IG) are represented by dashed lines. Participants in the usual care group (UC) are represented by solid lines.

For comparison purposes adherence to intervention for the three intervention group participants is as follows:

- IG1 between assessment 1 and 2, 58%, between assessment 2 and 3, 42%;
- IG2 between assessment 1 and 2, 83%, between assessment 2 and 3, missing (withdrew); and
- IG1 between assessment 1 and 2, 58%, between assessment 2 and 3, 83%.

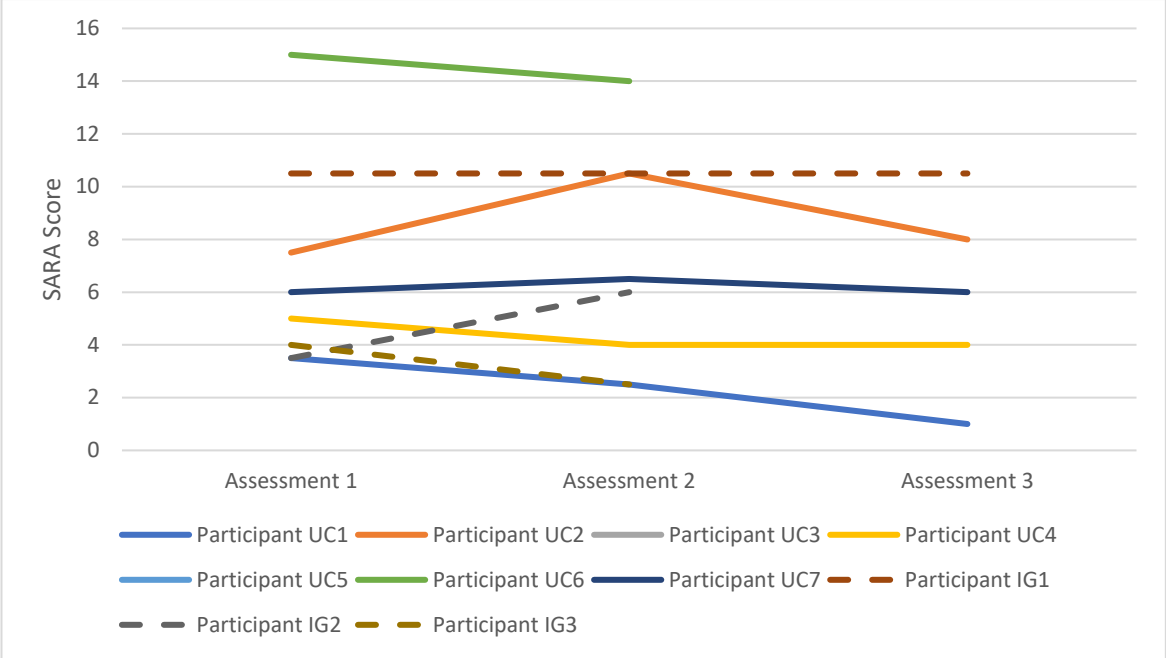


Figure 8.4 SARA score over three assessments for all participants

There are no obvious trends in results for SARA score assessed over time, with no evidence of consistent change in either usual care or intervention group participants. Two participants in the intervention group did not complete the full three assessments as previously stated (one withdrew at assessment 3 due to additional medical appointments, and one completed partial assessments over the phone as assessment 3 coincided with moving into the first lockdown as a result of COVID-19.) Two participants in the usual care group completed the SARA at two time points, and one participant (UC5) completed the SARA on assessment 1 only due to the impact of COVID-19. (A lower score represents improvement in ataxia).

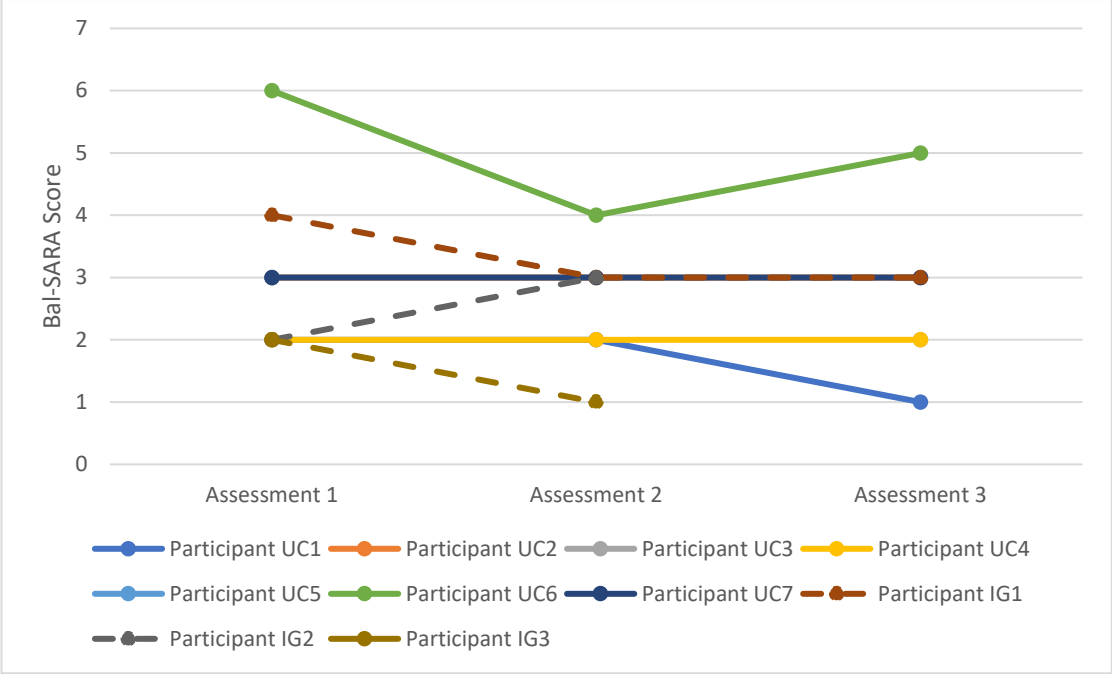


Figure 8.5 Bal-SARA score over three assessments for all participants

Again, no obvious trends are demonstrated for the Bal-SARA. Missing data is the same as for the SARA except one participant in the usual care group (UC 6) was able to complete the Bal-SARA as part of the SARA even though their full SARA score was incomplete for Assessment 3. (A lower score indicates an improvement in balance).

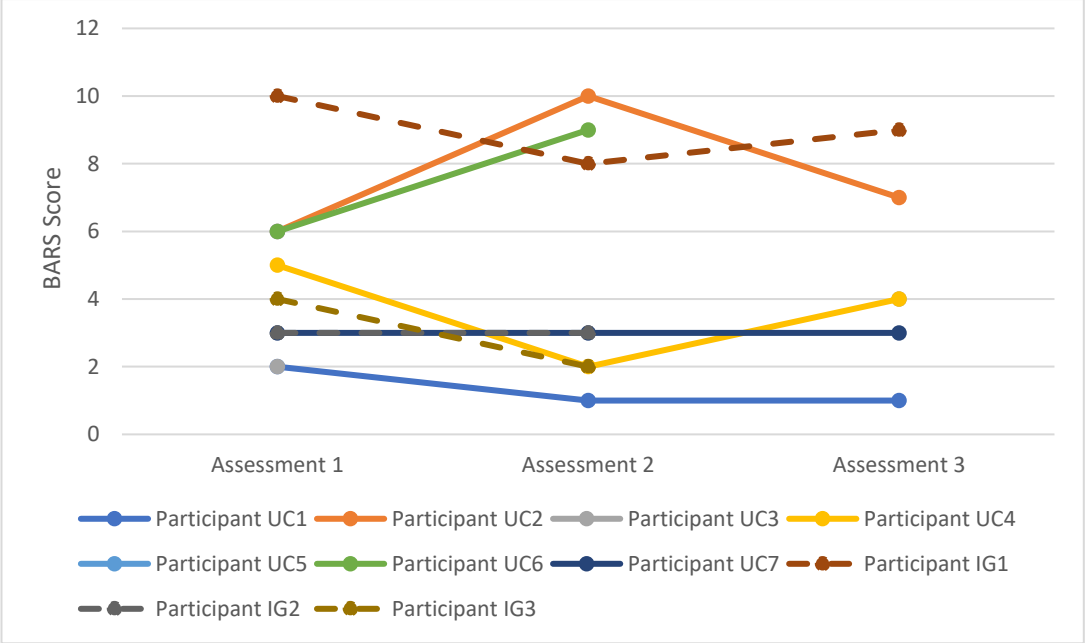


Figure 8.6 BARS score over three assessments for all participants

No obvious trends in change in BARS scores are demonstrated in either intervention or usual care participants. Missing assessments are similar to that of the SARA except for one remote video assessment the BARS eye item was not able to be completed whereas the SARA was fully completed. (A lower score indicates an improvement in ataxia).

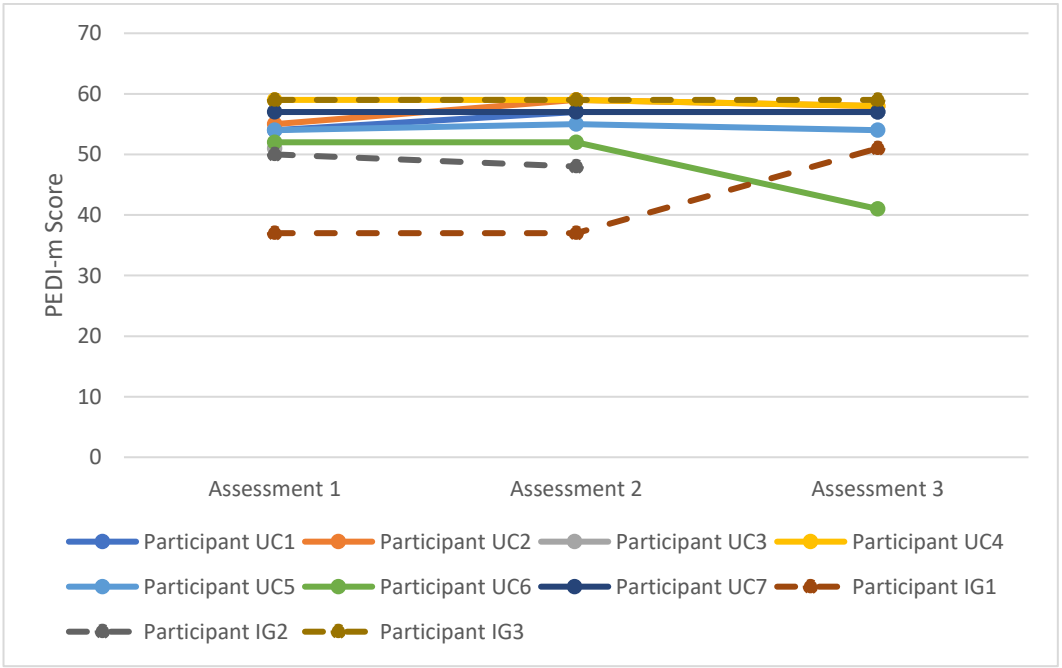


Figure 8.7 PEDI-m score over three assessments for all participants

Again, no obvious trends are demonstrated for the PEDI-m. A higher score indicates an improvement in function for the PEDI. Three participants achieved the full available raw score (of 59).

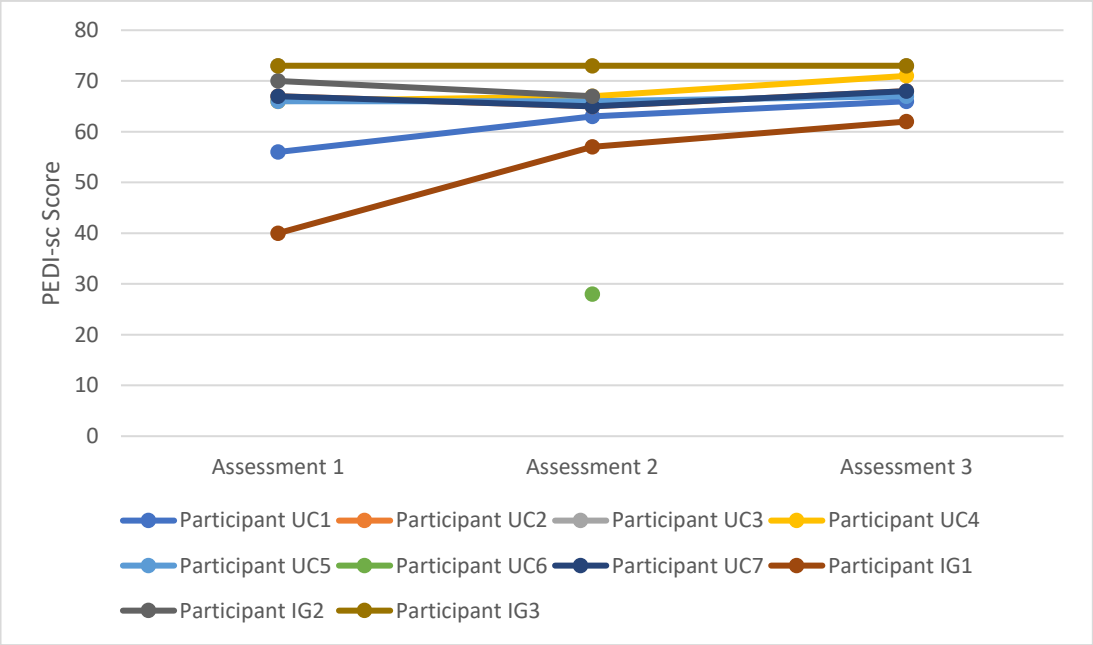


Figure 8.8 PEDI-sc score over three assessments for all participants

No obvious trends are demonstrated for the PEDI-sc. Again, for the PEDI-sc a higher score represents an improvement in self-care (includes items focused on washing and dressing). Only one participant achieved the full raw score of the PEDI-sc. For one participant in the usual care group (UC6) the PEDI-sc was completed on one occasion only. (Due to poor attention of the participant not all outcome measures were able to be completed within a reasonable timeframe for the assessment).

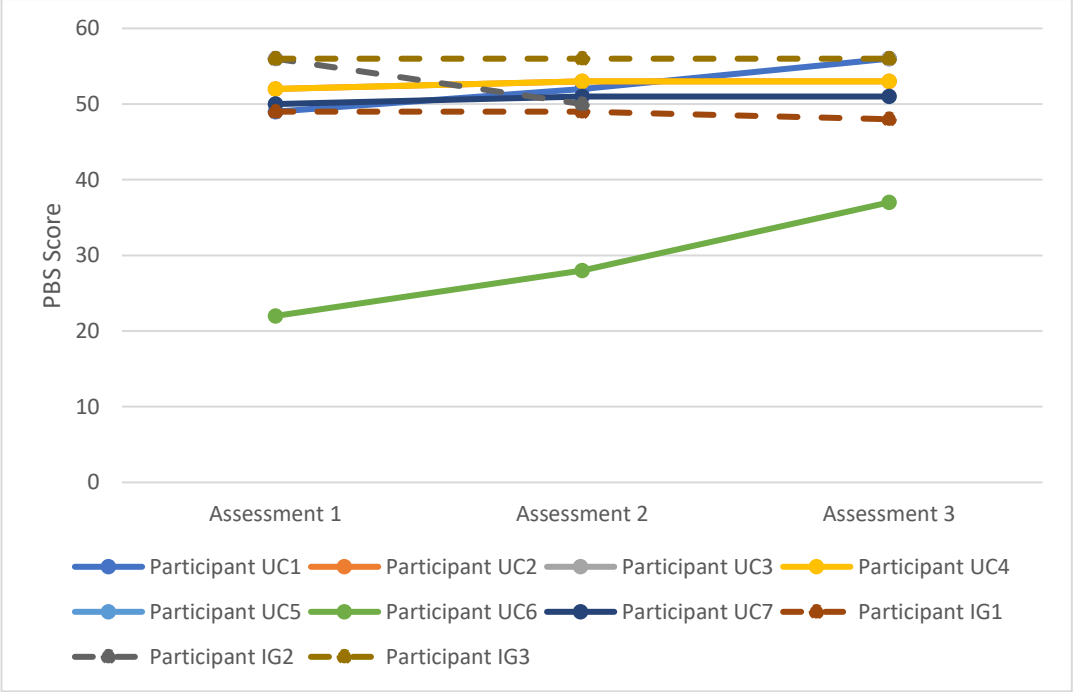


Figure 8.9 Pediatric Balance Scale score over three assessments for all participants

No obvious trends are demonstrated in the Pediatric Balance Scale scores. Three participants achieved the full score (56) indicating good functional balance. Items on the outcome measure include standing with eyes closed and single leg stance.

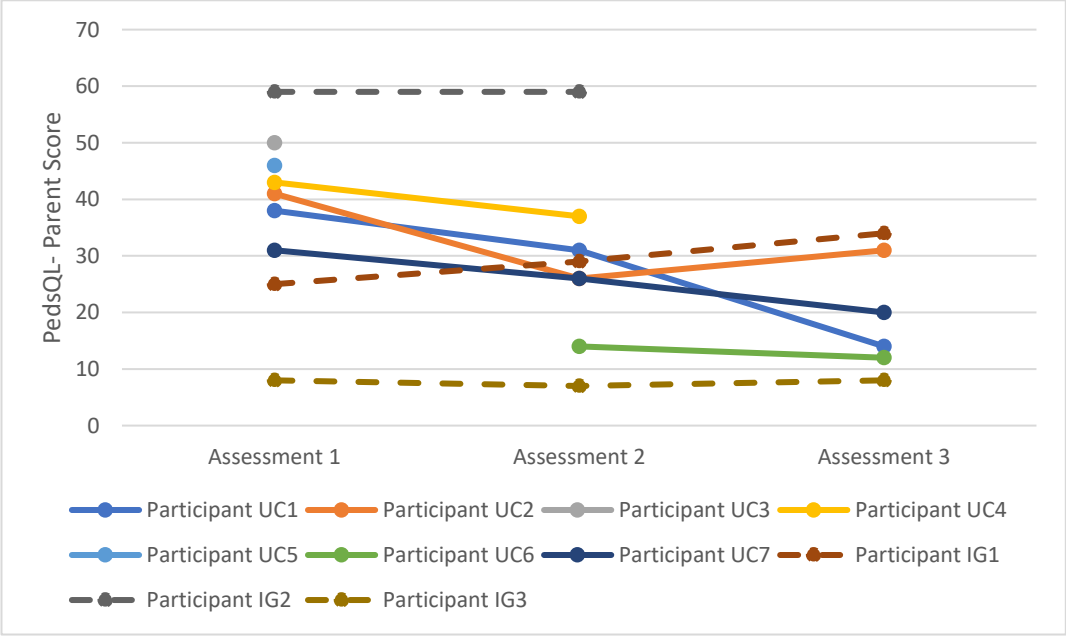


Figure 8.10 PedsQL-Parent score over three assessments for all participants

No obvious trends are demonstrated in the Peds-QL parental questionnaire outcome measure. The parent version is presented as this had been completed on more assessment time points than the child version. A higher score indicates worsening quality of life (measured across the following domains: cognitive problems, movement and balance, pain, procedural anxiety, nausea and worry).

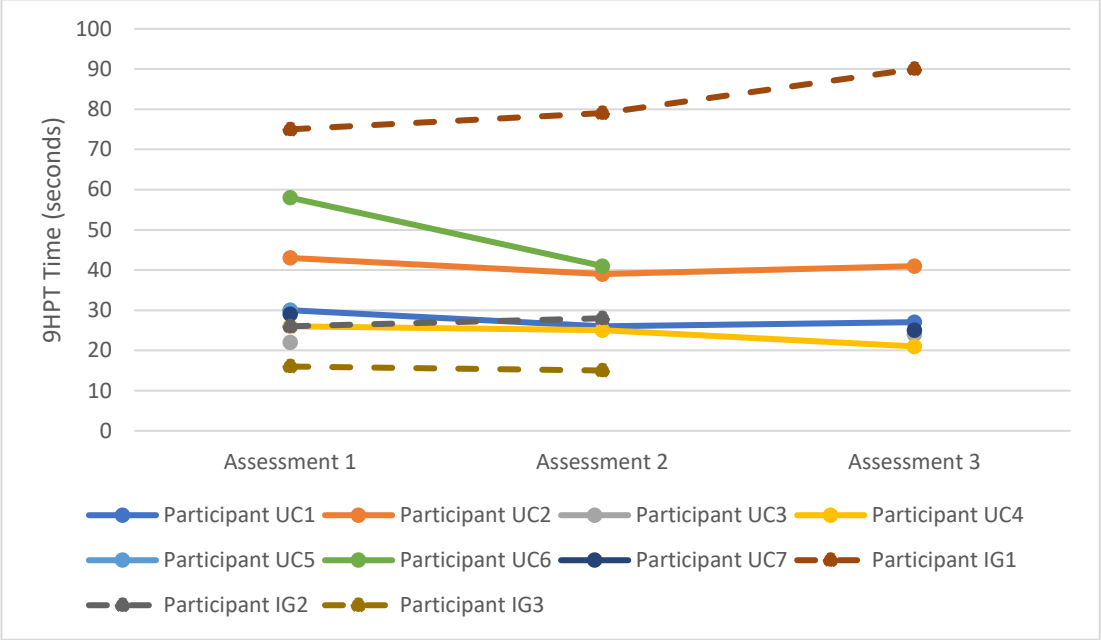


Figure 8.11 9 Hole Peg Test (dominant arm) score over three assessments for all participants

No obvious trends are demonstrated for the 9HPT. This is presented for the dominant upper limb, as more assessment timepoints are available for this compared with the non-dominant side. The 9HPT is a measured test, with a longer time to complete indicating more difficulty.

Table 8.8 Global Impression of Change

Participant	Assessment 2	Assessment 3
UC1	0	2
UC2	1	1
UC3	MISSING	0
UC4	0	2
UC5	0	0
UC6	1	2
UC7	0	0
IG1	1	0
IG2	1	MISSING
IG3	0	1

Table 8.8 indicates the child/parent impression of change of ataxia between assessments. 0 represents no change, 1 represents minimally better, 2 represents much better (Appendix 49). No participants reported a deterioration in ataxia.

Non-parametric tests to look for differences between groups were not completed for any outcome measure due to low numbers in each group with an uneven split between intervention and usual care group.

Sample size estimate

Utilising the CARS (Phase 1) data (in view of small numbers recruited to the feasibility trial to date) an example sample size estimate has been calculated for a definitive trial. This process will be repeated on full completion of the feasibility trial. A change of >2 for the SARA has been deemed clinically meaningful based on the CARS data.

For Phase 1 data the reduction in SARA at 3 and 12 months was 4.7 and 5.6 respectively. The standard deviations were 4.6 and 4.2 respectively. Using a difference of 3 between the intervention and control groups as clinically meaningful (i.e. in the intervention group we are expecting a reduction of 4.7+3=7.7 and 5.6+3=8.6 points in SARA respectively), based on 90% power 50 children would be required per group. Therefore 100 participants would be required in total, however, this does not allow for drop out, which would increase the required sample size slightly. For example, if we assume a drop-out rate of 20%, then the required sample size would increase to 125.

8.13.4 Findings from the embedded qualitative data analysis

In order to maintain anonymity as far as possible participants have not been identified as male or female in the qualitative analysis. Participants are labelled as UC1, 2, 3 etc. for usual care group and IG1, IG2, IG3… for intervention group. Parents of participants are identified as mother (M) or father (F) as follows F1-UC, M1- UC… and F1-IG, M1-IG etc.

8.13.4.1 Intervention group interviews

Three children were recruited to the intervention group and 3 children and 2 parents completed the intervention group interviews at the end of weeks 1 and 4 of the intervention (Appendix 50 shows example questions and prompts). The children were aged from 5-14 years of age, 2 were children who had been diagnosed with medulloblastoma and therefore had undergone surgical intervention and adjuvant oncology treatment (radiotherapy and chemotherapy). One child was diagnosed with a low-grade glioma and had solely undergone surgery as their treatment.

Initially child and parent data were considered separately for week 1 and week 4 before being then combined as a family set (where applicable). Following the generation of preliminary themes, the data were then considered as separate data sets. The themes were then reviewed and are presented below. Due to a small data set a simple descriptive analysis was undertaken.

Sense of enjoyment

The children all reported a sense of enjoyment undertaking the training within the hospital setting. It was reported as *"fun"* both at the end of week 1 and with ongoing positive feedback at the end of week 4, with one participant (IG2) describing the training at the end of week 4 as *"good, amazing, a bit hard but I like it".* The children were able to identify games that they enjoyed the most (and those they did not like), different participants selected different games, highlighting a variety of choices to suit different age ranges and abilities. Parent feedback was also positive, with one mother (M2-IG) reporting, *"excellent, reinvigorating them with physio"* and another stating that her child had *"really enjoyed it, it's been lovely to watch them enjoy it"* (M1-IG).

Progression

The children reported differing opinions as to whether the training became harder or easier over the 4-week period. One child (IG1) provided feedback that the training at week 4 was

easier, but it was reported as harder by another child and their parent. Children and parents observed that the games could be progressed and adapted as needed, one mother (M3-IG) stated that games were at an 'appropriate level' for her child who had *"progressed games up and down"* according to fatigue.

Ease of use

Again, differing opinions were expressed regarding ease of use of the Xbox Kinect. One child (IG1) and their parent expressed frustration that due to upper limb ataxia it was *"difficult for the sensor to pick up at time – frustrating"* (M1-IG). Whereas another participant (IG3) reported no issues with using the virtual training *"setting up the Xbox was easy"* (IG3), highlighting that different physical presentation may impact on ease of use.

Burden

Although the children provided feedback that they did not mind attending the hospital, parents highlighted the challenges of attending the hospital for the 4-week programme. At the end of week 1 attending for three times a week was felt to be 'about right' but on the week 4 interviews the same parent (M2-IG) reported *"4 weeks was achievable but any more would have been a struggle as has made compromises i.e. school."* This highlights the challenge of balancing the intensity of training with other commitments.

Fatigue/coping strategies

Fatigue was raised as an issue by two parents in the week 4 interviews. They reported their own strategies that they were using to accommodate this, e.g., one parent (M3-IG), explained they had a *"carefully planned diary"* and were *"not doing other activities when attending the hospital".* Parents were also mindful of scheduling in rest periods for their child to help them to cope with the length of the sessions with one parent noting that their child *"needs to take breaks, but [was] determined to carry on"* (M2-IG). Fatigue was not specifically raised by the children although one child (IG2) said that during week 4 they

found that *"walking and school was difficult";* this had not been reported at week 1, possibly reflecting similar challenges to those observed by the parents.

8.13.4.2 Exit interviews

Seven parents completed the exit interview (5 face to face, 2 virtually), with two children also providing some comments during the interviews. Five parents and one child were from the usual care group and two parents and one child were from the intervention group.

Completed participant diaries were also reviewed as part of the data analysis to add further insight. This analysis was a comparison of quantitative data reporting fidelity to the intervention and a record of other exercise undertaken by participants.

Three main themes, overarching across both groups, were identified and then specific themes relevant to the intervention and usual care group were also identified (Figure 8.4). It is worth noting that overlap was evident between themes identified in all the intervention group participant interviews (weeks 1, 4 and exit).

CROSS CUTTING THEME (Intervention & Usual Care)

- Motivating factors (helping others, familiarity with research)
- Child/parents-centred demographics (level of activity, family situation)
- Acceptability of assessments

INTERVENTION GROUP THEME

- Sense of enjoyment
- Burden
- Fatigue

USUAL CARE THEME

- Reassurance
- Acceptance of randomisation

Figure 8.4 – Thematic map of themes identified from participant/parent exit interviews

Cross cutting theme Intervention and Usual Care

Motivating factors

Motivating factors, and barriers to participation were raised by parents in the exit interviews. Typically, there was a sense of wanting to help, one mother (M6-UC) stated *"if you can help by doing these studies, and that can inform decisions on proven treatments and outcomes then you know that's absolutely the reason"*, another mother (M3-IG) responded that *"they wanted to help others"*. This was supported by a father (F1-UC) who explained *"we always said if we could help other children we would"*. There were also personal motivating factors acknowledged from wanting to help their child, one mother (M7-UC) replied *"you know just wanted to see if it would help them"*. A child wanted to complete their participation so that it could contribute to their Duke of Edinburgh award. Overall, there was positive feedback regarding the study, one mother observed *"it was fine, it was easy enough"*, and another provided feedback that their child (M1-IG) enjoyed attending so much that *"[child] did a physio dance when I said [child] was coming here today"*. Completion of the study was occasionally impacted by other medical conditions, especially if more appointments were required for other reasons. One father (P2-UC) highlighted *"it was a bit difficult at this time [in between assessment 2 and 3], because of the other visits we had to do, we just couldn't commit any extra time"*. Favourable responses were noted when appointments were flexible to the demands of child and family commitments and one mother (P1-UC) highlighted that *"all the appointments were in school holidays so that was great".*

Child/parents-centred demographics

A mix of responses regarding pre-existing level of activity and experience of physiotherapy was noted in the exit interviews. Generally, families taking part in the study reported undertaking a range of activities, feeling they were quite active. One father (F4-UC) stated *"we have such a busy life anyway don't we",* and a mother (M7-UC) reported that her child, *"does things on zoom Monday to Friday after school, has a lot on"*. The type of pre-existing physical activity varied and was adapted for any fatigue experienced by the children, but a

range was observed including dance, swimming and football. Only one family reported using gaming for physical activity, with the mother (M7-UC) explaining that her child is *"using the ring fit, [and] really enjoys it"*.

Parents were able to reflect on their diary completion and potential impact of this on their activities during the study period. One mother (M1-UC) reported that *"we [referring to her partner] got used to filling it in, it's a bit like having the teddy bear from school – you know you have to do something really good"*. Another mother explained *"we filled it in – in a lot of detail"* (M7-UC). However, not all families returned their diaries with one set of parents noting they had done it but had forgotten to bring with them despite receiving postcard reminders.

The parents reported different experiences of physiotherapy. Some families were still known to local therapy services but generally were being seen less frequently, one mother (M1-UC) acknowledged that their child *"sees them [therapy services] every 3 months, programme is done in school"*. Others reported being discharged from their local team and although there was a sense of reassurance of having contact with the Tertiary Centre (see later), the lack of community therapy input was not raised specifically as a reason for participating. Other parents reported having a home exercise programme but compliance with this was reported as being variable; one mother (M4-UC) stated that her child *"has those exercises, just had a little go, just depends on what else is happening, how tired [child] is"*.

Acceptability of assessments

Overall, there was a positive response regarding the length and number of assessments. Typical responses from parents included *"yes they went through really quickly" and "copes with it fine"* (M1-IG). The children seemed to find the assessments familiar also with one child (UC7) reporting *"I knew what was coming next"* and the parents also acknowledged that they were similar to usual assessments with one father (F2-UC) reporting the

assessments *"were fine, weren't too long, similar to what they've done before anyway"*. Only one family found the visits for assessments difficult when other medical issues had arisen resulting in additional visits to the hospital unrelated to the study. The majority of parents expressed an interest in the results and also requested a copy of their child's assessment findings.

Only two children were recruited after the first wave of the COVID-19 pandemic which meant they could engage via video assessments. However, both families expressed a preference for face-to-face assessments believing they offered more for their child, one mother (M6-UC) stated her child was *"more receptive to that, gets more out of it",* another mother agreed (M7-UC) *"you can see better what [child] can do"*. They also highlighted the challenges of video assessments noting that *"I end up running round with the iPad trying to get [child] to perform, and it never turns out that way"* (M7-UC).

Experience of intervention group

Experiences of the parents and children in the intervention group that were raised in the exit interviews identified sense of enjoyment, burden and fatigue. Even though only a very small number of views were gathered, this information did add insight into these areas.

Sense of enjoyment

Again, a positive response to playing the games was conveyed. It was highlighted that the individual children had specific games they enjoyed the most and this seemed to link with the things they did well at. One mother (M1-IG) reported that her child's *"favourite was the pancake one, was really good at it"*. When asked if they liked their normal physiotherapy or the games the best, one child (IG1) reported *"the games"*. A potential benefit from a cardiovascular perspective was also raised by one parent (M3-IG) who observed that *"the cardio ones [games] were still pushing [child]"*. Although a sense of frustration was also noted that one football game was not similar to the real thing, and one mother (M3-IG) stated *"but with the game, couldn't get it to respond how wanted to".* Parents of both IG1

and IG3 used strategies to continue with the training at home by involving family members e.g. grandparents and siblings.

Burden

Although the parents reported they felt the number of sessions at the hospital and then at home was acceptable, noting that *"the mix was fine really I understand why it was like that"* (M1-IG), both did express that it would have been easier if more training was at home. Although overall face to face assessments were felt to be reassuring, considering the number of visits required for the intervention training, parents felt more could have been completed at home. One mother acknowledged (M3-IG) "*for us, that would have suited us, really once they had showed us, once we knew what we were doing"* and another mother (M1-IG) highlighted the challenge of travel stating *"if it [intervention] was at home it would be ok, I guess the coming in is difficult"*. Analysis from participant diaries and interviews shows that the median training per week at home was twice a week, (range 1-3 on individual weeks); this was under the targeted three times a week for the four-week home training period. Although the setup of the Xbox was reported to be easy, issues with space at home were raised as a barrier to use in the home setting by one mother (M1-IG) who noted that it is *"difficult to get far away [from the sensor]"* and they had to seek alternative strategies such as playing it at a relative's house.

Fatigue

Fatigue was again raised in the exit interviews by the parents of participants in the intervention arm. This seemed particularly exacerbated when there was a longer distance to travel. One mother (M3-IG) stated *"it was tiring, as I said we are an hour and half away and if it was earlier following [child's] surgery we couldn't have done that many trips – although we were at the hospital more often then, wouldn't have coped with it*". Typically, appointments were completed in the afternoon to minimise loss of school time although this meant completion of training after the school day. As noted in the intervention interviews families naturally began to adopt their own strategies to pace activities and one mother (M3-

IG) disclosed "*we just had to make sure it was planned quite well, we got there had a drink, did the session and came home"*, and she also stated *"if [child] was due to attend [child] didn't do PE that day, so it was just careful planning really"*. Parents also said that this level of training would not have been possible early post-surgery, one mother acknowledged *"I think if it was something they did just after surgery wouldn't have coped with it"* (M3-IG).

Experience of usual care group

Reassurance

Although children allocated to the usual care group only underwent assessments, parents expressed a sense of reassurance of being monitored by the Tertiary Centre. One mother (M1-UC) stated *"we were actually like, even though they were just assessments for us, they were another dose of physio"*, and this was echoed by another mother (M6-UC) who said *"I felt that, you know what, either way it's extra physio, it's an extra eye"*. This appeared to be linked with a sense of confidence of ongoing contact with the Tertiary Centre amidst concerns regarding transition to community services and the lack of services. One father (F1-UC) stated *"the acute physios here [Tertiary Centre] are better trained in dealing with the condition"* and another mother (M7-UC) reported in relation to local therapies that *"they have just discharged them, without seeing them"* and another father reported that the *"'physio was off, so didn't have much physio"* (F2-UC).

Acceptance of randomisation process

Overall, there was an acceptance of the randomisation process by the parents of participants in the control group. Parents appeared clear about the randomisation process, with one father (F4-UC) stating *"we knew up front that it could go either way so it was fine really"*, another response mirrored this (M7-UC) *"it was fine not doing it"* with a third highlighting they felt there were benefits anyway "*even though in control group would still benefit"* (M6-UC). However, although there was a general acceptance of this process one parent expressed disappointment, *"really, we did want to see if the video gaming would*

help" (F2-UC). Another parent (M6-UC) acknowledged that even though they were *"OK"* with the process, they were not sure whether if their child was older and had an insight into the implications of potentially having more gaming time whether they would have then been disappointed, observing that *"again [their] age, doesn't know any different, had been older and thought I could get extra time on the consoles that might have been different"*.

8.13.5 Integration of the qualitative and quantitative findings

The purpose of integration is to address the specific objectives of the study and therefore the integrated findings are framed in terms of the feasibility of the RCT design, and the feasibility of the intervention (including adherence, experience, acceptability and practicality). Agreement between quantitative and qualitative findings is presented alongside insights and potential strategies to address any feasibility issues. The integrated findings regarding feasibility of RCT design are presented in Table 8.9.

Table 8.9 Integrated findings; feasibility of RCT design

Topic	Quantitative	Qualitative	Level of agreement	Insights/Strategies
Burden of trial	Recruitment rate 6-40% (site dependent; Site 1: 8 out of 20 Site 2: 1 out of 17 Site 3: 1 out of 4 Site 4: none approached Total 10 recruited out of the 41 eligible children).	Travel burden negative impact. Time commitment for intervention negative impact (Exit interview n=2 parents)	Agreement	Recruitment rate under set 'go criteria'. Need for increase resources/time for PI on other sites to optimize. Consider intensity of intervention and mix of home/clinic appointments in future. Alternative options to trial design include n=1, or single arm intervention which would increase findings re VRT (but at expense of RCT design).
Burden	40% diaries returned.	No issues with diary completion reported in interviews. (Exit interview n=3 parents)	Agreement	Diary return rate satisfactory, could consider electronic options to try and increase return.
Willingness for randomization	Drop out following randomization (n=0).	Acceptance of process going into study.	Agreement	No issues.
Acceptability of assessments	Median assessment length 70 minutes.	Children familiar with assessments, no issues. (Exit	Agreement	No issues with assessment protocol.

	Completed all assessments (n=8).	interviews n=5 parents)		Remote video assessments also now available, require ongoing evaluation.
Acceptability of outcome measures	Peds QL child not completed 6/24 face to face assessments. PBS completed for each F2F assessment. SARA, BARS completed for 23/24 F2F assessment.	Children familiar with assessments, only issue with language on PedsQL.	Agreement	Outcome measures acceptable. Choice of outcome measure for future trial remains under review. Remote video assessments require ongoing evaluation.

F2F= face to face

Integration of the qualitative and quantitative data enables the reasons for low recruitment to be understood, in terms of study burden and commitment. The qualitative findings also support the willingness for randomisation that was noted in the feasibility process measures. Qualitative feedback regarding the assessments provides confirmation of the acceptability of this element of the study.

Integrated findings regarding feasibility of the intervention are presented in terms of adherence/experience and acceptability in Tables 8.10 and 8.11.

Table 8.10 Integrated findings; adherence/experience of intervention

Topic	Quantitative	Qualitative	Level of agreement	Insights/Strategies
Ability to use intervention (VRT) in hospital setting (Therapist reported)	No. of hospital-based intervention sessions completed, (median 7).	Easy to set up. UL ataxia can increase difficulty in selecting games. (Embedded intervention interviews n=1 parent).	Agreement	No significant issues, all participants able to use. Continue to record in context of differing ages/abilities
Ability to use intervention in home setting (Parent reported)	No. of home-based sessions completed, (median 2 per week).	Children familiar with technology. (Embedded intervention interviews n=1 parent, n=1 child, exit interviews n=1 parent).	Agreement	No significant issues, all participants able to use. Continue to record in context of differing ages/abilities
Barriers to use intervention in hospital setting	No. of hospital-based sessions completed, (median 7).	Children familiar with technology. Difficulty with attending x3 a	Agreement	Concerns regarding frequency of attendance. See if option of remote

(Parent/child reported)		week (travel/family commitments). (Exit interviews n=2 parents).		appointments increases adherence
Barriers to use intervention in home setting (Parent reported)	No. of home-based sessions completed, (median 2 per week).	Limited space is a barrier. Participation with family members increased compliance. (Exit interviews n=1 parent).	Agreement	Under target for home sessions. Consider strategies to increase participation similar to those used to increase adherence to home exercise programmes.
Safety/adverse events	1 non serious adverse event recorded.	Fatigue reported by children. (Exit interviews n=1 parent). Pacing strategies employed.	Agreement	Low number of adverse events. Continue to record.

Table 8.11 Integrated findings regarding acceptability/practicality of intervention

Topic	Quantitative	Qualitative	Level of agreement	Insights/strategies
Enjoyment	No. of hospital-based sessions completed, (median 7).	Fun to use. (Embedded intervention interviews n=2 children).	Partial Agreement, (positive feedback but adherence remained under target both for hospital and home sessions).	No issues Continue to record.
Game preference	Games ranked most enjoyable.	Negative feedback from child if game difficult. (Embedded intervention interviews n=1 child). Variety of games chosen as favourite.	Agreement	To date game options available to suit wide age range of participants.
Practical to use at home	1 non serious adverse event recorded. No. of home-based sessions completed,	Limited space can be a barrier. Children familiar with technology to set up. (Exit	Agreement	Low number of adverse events with all participants able to use at home. Continue to record.

	(median 2 per week).	interviews n=2 parents).		
Intensity of intervention	No. of hospital-based sessions completed, (median 7). No. of home-based sessions completed, (median 2 per week).	Time commitment a challenge. Fatigue with combination of travel and intervention. (Exit interview n=1 parent).	Agreement	Intensity of intervention needs further consideration, check this again with option of remote video intervention sessions. Consider adding fatigue outcome measure in future.

Again, integrating qualitative and quantitative data provides insights into the compliance and adherence to the intervention which would not have been achieved just by the quantitative findings. Parents' explanations of travel and time burden and issues with their child's fatigue help to generate understanding about lower adherence to training.

Integrating the findings also indicates that there are a number of inter-related constructs such as, e.g. recruitment can be affected by both RCT design and the intervention protocol. Furthermore, adherence to training can be influenced by both the intervention protocol and feasibility of using the intervention itself. These interrelationships highlight the difficulty in balancing robustness of research design alongside determining a training protocol that is acceptable to families whilst being intensive enough to drive a possible meaningful change. These factors are considered further in the following discussion.

8.13.6 Overall assessment of feasibility

Although the study is continuing and any final feasibility recommendations will be reviewed at the end of the extended recruitment period, preliminary assessment of overall feasibility has been considered. Recruitment rate was below the 'go' criteria pre-specified for the study however, there was low drop out and high completion of assessment time points and minimal issues with the outcome measures which were the other pre-defined criteria. This suggests potential to continue with the study with possible refinements to optimise recruitment and increase acceptability of the burden of the intervention group.

Young et al. (2019) presented pre-specified progression criteria for an adult exercise-based feasibility trial in five areas; eligibility, recruitment, intervention acceptability, outcome acceptability and loss to follow up. Although these criteria were developed specifically for Young et al.'s (2019) trial, if adopting this framework for Phase 4 the stop criteria was only demonstrated once for specific sites (Site 2-4) in terms of recruitment. The comparison between Young et al.'s (2019) progression criteria and the results of the ASPECT feasibility trial are presented in Table 8.12.

Table 8.12 Comparison between Young et al.'s (2019) progression criteria and Phase 4 results

Criteria	Young et al.'s 2019 criteria	ASPECT Study results
Eligibility	Stop: < 20% of participants eligible. Go: > 50% of participants eligible.	Site 1 28% Site 2 44% Site 3 50% Site 4 Not known Total 41 eligible out of 143 children identified.
Recruitment	Stop: < 25% of eligible participants recruited. Go: > 50% of eligible participants recruited.	Site 1 40% Site 2 6% Site 3 25% Site 4 0% Total 10 recruited out of the 41 eligible children.
Intervention acceptability	Stop: < 30% adherence to intervention sessions. Go: > 70% adherence to intervention sessions.	42-83% adherence (Average 66% adherence to hospital-based intervention, average 62% adherence to home-based intervention).
Outcome acceptability	Stop: <70% outcome measures completed. Go: > 80% outcome measures completed.	80% of assessments completed. All outcome measure completed in 63% of face-to-face assessments. Excluding the PedsQL, all other outcome measures completion >80% (face-to-face).
Loss to follow up	Stop: > 40% loss to follow up. Go: < 20% loss to follow up.	10% loss to follow up/withdrew

Determining acceptability was also a specific objective for this study as part of establishing feasibility. A framework of examining acceptability has been proposed by Sekhon et al. (2017) highlighting that acceptability consists of seven constructs: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-

efficacy. Whilst using this framework was not the focus of the results reporting it is observed that multiple constructs were demonstrated in the results e.g. affective attitude (positive feedback regarding the intervention), self-efficacy (high adherence/no issues with the assessments), intervention coherence (parents understood the nature of the RCT design), perceived effectiveness (parental thoughts that the study might help their child), ethicality (desire to help others by participating). The only construct where concerns were raised was 'burden' with previously highlighted issues regarding commitment to the intervention arm in particular.

8.14 Discussion

8.14.1 Synthesis of results

This study has provided new information regarding the feasibility of conducting a RCT examining VRT in children with ataxia following surgical resection of a PFT. Information regarding process, intervention and assessment measures was gathered with the incorporation of an embedded qualitative component to help understand the quantitative findings and to explore child and parental views of the intervention. There was agreement between the qualitative and quantitative findings, thus providing a depth of understanding of the feasibility measures.

The assessment schedule and outcome measures appeared feasible to complete although there were challenges to recruitment for the trial. Concerns regarding the intensity of the intervention and thus commitment required to participate in the trial, along with the impact of COVID-19 led to below target recruitment. No firm conclusions can be made about the intervention due to small numbers in the intervention arm. However, the children who participated, provided positive feedback regarding the VRT and no serious adverse effects were identified which is in keeping with related literature, e.g. for children with cerebral palsy (Ravi et al. 2017, Chen et al. 2018).

There is a particular lack of guidance regarding defining stop/go (or progression) criteria for feasibility studies (Mbuagbaw et al. 2019). However, overall elements of feasibility have been demonstrated and these have been linked to example criteria proposed by Young et al. (2019) and a framework for acceptability (Sekhon et al. 2017). Considering the previously set stop/go criteria for proceeding with a definitive larger trial, the recruitment rate did not meet the selected target, with the onset of a pandemic inherently detrimentally affecting recruitment and percentage drop out. However, acceptability/completion of outcome measures were satisfactory. Therefore, there is potential to continue with research in this field, although further examination of aspects such as optimising recruitment strategies, refining intervention intensity, optimising the balance of home and hospital-based training, and considering when the child is ready to train independently at home, is required before planning a larger scale RCT.

8.14.2 Feasibility of RCT design

The next section will focus on key elements of feasibility of the RCT design, with challenges to recruitment, use of outcome measures and issues of the research design itself discussed in more detail. These elements inform the specific study objectives relating to process measures and selection of outcome measures.

8.14.2.1 Challenges to recruitment

There are several factors that contributed to lower than expected recruitment. These included lower than the expected number of participants identified, site specific issues, participant demand/acceptability of the study protocol and the impact of COVID-19. These factors will be discussed in further detail.

Initial identification of potential participants at the first two sites was lower than anticipated. This was highlighted early, and other sites were approached (and later opened) along with a revision in recruitment target to account for this. Prior estimates for potentially eligible participants were calculated from pre-existing databases which record the number of

children with posterior fossa tumour presenting at the tertiary centres. Although the overall number of children with PFT was in line with expectations, the number of children excluded was higher than anticipated. E.g., the main host site identified 71 children with PFT, but 51 children were excluded.

During the first year of recruitment, it was observed that a number of children were excluded due to SARA score under 2 (i.e. no significant ataxia). However, over the whole study period, children excluded due to no significant ataxia was in keeping with expectations. Thirty two percent of children were excluded as their SARA score was under 2 for Site 1 similar to Site 2 (33%). This is in keeping with the literature as previous research observed that 30% of children with PFT do not have any long-term balance problems (Piscione et al. 2014, Hartley et al. 2018). Although it was noted by the study team that fewer children were presenting with 'severe' ataxia, this may be linked to a general reduction in cerebellar mutism syndrome (CMS) seen internationally, which has been reported by the interim results of the NORDIC study (Gronbaek 2021). This is thought to be due to increased awareness and surgical planning. CMS is often linked with presentation of more severe ataxia (Hartley et al. 2018). This could have impacted recruitment as parents of children with fewer physical functional difficulties may not have seen participation as a priority.

Other reasons for exclusion included children being aged under 4 years (16), and for the host site 14 children (20%) were not approached due to relapse, this was higher than expected. Overall, the inclusion percentage following screening was: Site 1 20/71 (28%); Site 2 17/39 (44%); and Site 3 4/8 (50%), Site 4 unknown. Although variation was shown between sites, the inclusion rate following screening was lower than the anticipated 50% across sites, this was particularly evident at Site 1 (28%). The pre-existing information this 50% rate was based on possibly did not factor in the number of children who might relapse or require further neurosurgical/oncology intervention at a later date. This raises questions about inclusion criteria for future studies, meaning that a wider time range following surgery could be considered, e.g. that is, not restricted to 1-3 years following surgery. It is clear that

in a future study the number of sites needed to achieve the required number of eligible participants should be considered carefully.

In addition to the study being suspended to recruitment due to COVID-19 (for five months at Site 1, ten months at Sites 2 and 3), thus impacting on the recruitment timeframe, there were specific site issues which shortened time frames for recruitment. E.g., there were delays through local approval processes both in the first instance and on reopening following suspension due to COVID-19. Even though the required recruitment rate for the study appeared low, this rate was still not achieved. This was despite both the revised lower target for recruitment and the length of time each site was open for. The recruitment percentage (i.e. % recruited from number of children identified as eligible and approached) was variable between sites e.g. 40% for Site 1 (8/20 40%), 6% for Site 2, (1/17 to date), 25% for Site 3 (1/4), and Site 4 did not recruit due to lack of therapy capacity secondary to the second wave of COVID-19. Whilst under recruitment is not uncommon and has been reported extensively in the literature (Kaur et al. 2012, Walters et al. 2017) with particular reference to challenges recruiting adolescents with cancer (Fern & Whelan 2010) (typically referring to drug related trials), understanding the variance in recruitment for each site might also help future trial planning. The highest recruitment was observed in Site 1, as the host site there was specific trial coordinator time available along with therapy presence in follow up neuro-oncology clinics to enable discussion about the trial with the families. This is in keeping with evidence that the largest barrier to recruitment from a centre perspective is lack of time and resources to dedicated to research (Isaksson et al. 2019). In the other site's recruitment was reliant either on parents initiating contact themselves following receipt of written information or other professionals in consultant led clinics. Site 2 was recognised as having a particularly low recruitment, and it was noted that the consultant led clinic attended by families who might be interested in the study was held on a different site. Therefore, to allow further discussion and PI presence at this clinic, the Trust where the clinic was held was added as a Participant Identification Centre (PIC). However, the approval was granted

for this after the suspension for COVID-19 and Site 2 was delayed in reopening due to local capacity so it was not possible to establish if adding the PIC would increase the recruitment. In the future ensuring relevant funding for a trial coordinator post with time to approach families and have face-to-face discussions regarding possible recruitment would be of value. The small number of children recruited post COVID-19 (and shorter time frame for recruitment) meant it was not possible to draw any conclusions as to whether recruitment was higher or lower post COVID-19. The two families that were recruited at Site 1, post COVID-19, reported that they had not seen their local therapy team as often due to COVID-19 and were keen to keep links with the Tertiary Centre. However, local capacity due to redeployment of therapists at Site 4 impacted on recruitment post COVID-19 so it unclear if recruitment following reopening was impacted positively or negatively following the pandemic. This may become clearer with the ongoing data collection which is not part of this thesis.

Recruitment for this study is lower than reported in other similar studies. Sabel et al. (2016) note that 13 out of 16 participants (81%) were recruited in a home based VRT trial in children with brain tumours, and Baque et al. (2017) report 60 out of 77 participants identified (78%) were recruited to their RCT for children with ABI which had a longer intervention time (20 weeks) than this study. Comparing studies with protocols similar to this study (Phase 4) specifically focused on ataxia and with a mix of home and clinic-based training, Schatton et al. (2017) reported an enrolment rate of 10/14 (70%). However, other similar studies do not specify recruitment percentage/rate (e.g. Ilg et al. 2012). A cross over design study by Piscione et al. (2017) with children with brain tumours exploring exercise in a group and community setting presented a low recruitment percentage that is comparable to Phase 4 with 28 out of 96 (29%) eligible participants recruited. Therefore, there appears to be significant variation in recruitment, regardless of length of trial, or whether it is clinic or home based. If a longer recruitment period had been available post COVID-19 with the

introduction of remote assessments and interventions, it would have been interesting to see if the option of remote appointments increased recruitment.

Reasons for not entering this study were recorded (if given) and included, time commitment required and travel distance. These barriers have been observed previously (Prescott et al. 1999) and may be particularly relevant when undertaking intervention in rare conditions which result in a large geographical area of recruitment which makes travel to and from the Tertiary Centre difficult. Whilst there is no firm evidence base to suggest that 'incentives' such as payment of expenses lead to increased recruitment (Bower et al. 2014), additional travel costs have been perceived to be a barrier to recruitment (Prescott et al. 1999, Kaur et al. 2012). It was observed that travel time for participants to their study site varied from 15-90 minutes. Travel expenses were provided in this study but were not available immediately unless the family were attending the host site which was not ideal. Further consideration of health inequalities will be important in the planning of any future larger RCT.

One family felt that at this time in the child's development the focus was moving away from physiotherapy and towards education. They wanted to reduce visits to the tertiary centre and their aim was 'normalising life'; this again raises the question regarding whether the inclusion criteria were too restrictive. Although expanding the inclusion criteria to more than three years post-operatively as suggested above may increase potential participants, it might be that parents whose children are more three years post-surgery are less keen for their child to spend additional time out of school by participating in a trial. These reasons for not participating are in contrast to the parents' altruistic reasons for entering the trial as gathered in the exit interviews when parents reported their desire to help others. It has been reported previously that altruism motivations are common for both adults with cancer and parents of children with cancer participating in clinical trials (Truong et al. 2011).

In addition to a sense of wanting to help others, some parents sought the reassurance of contact with the Tertiary Centre. This was highlighted as a theme in analysis of the usual care group who reported that the assessments as part of the trial helped to monitor any issues and were happy to increase visits to understand more about the difficulties their child was facing. This 'self-interest' reason for participating (e.g. closer follow up, and improved attention) has been reported in cancer trials particularly related to drug treatments (Nurgat et al. 2005) but does not appear to have been reported in relation to rehabilitation studies.

Overall, striking a balance of minimising commitment and travel to make the trial acceptable, whilst ensuring the intervention has the potential to make a change in children is an ongoing challenge. Ensuring careful scheduling of appointments and offering flexibility regarding after school visits and timing with school holidays will also be key if considering a fully scaled trial. Whilst concerns regarding children missing school have not been reported extensively as barriers to clinical trial recruitment, these concerns are noted in the literature examining attendance and barriers to physiotherapy appointments in routine practice (Phoenix et al. 2020), and thus do seem important to consider. Typically, concerns reported as barriers are referred to with only an overarching consideration of practicalities of undertaking a trial (Bower et al. 2014). In this study, whilst the spacing of assessments allowed assessment appointments to be carried out in school holidays, which was reported positively by the families, intervention appointments, unless undertaken over the summer holiday period, would require time out of school. This is in keeping with the time commitment for the intervention group being raised as a reason for declining the study.

8.14.2.2 Outcome measures and the acceptability of assessments

Overall, the length of the assessments were feasible and acceptable to the children and their parents, and this was identified as a theme across all participants. No parents (or children) reported any issues with the assessments. Parents observed their children were familiar with the activities completed. The average length of the assessments was 70

minutes, which is just slightly longer than a typical physiotherapy appointment. The first assessment was the longest as the INAS was also completed on the initial visit.

The combination of ataxia, balance, upper limb, functional and quality of life outcome measures attempted to encompass the entire spectrum of the WHO framework of impairment, activity and participation domains, and is similar to other recent trials where a battery of measures was chosen (e.g. Peri et al. 2019, Baque et al. 2017). Despite this battery of measures, there is no specific participation measure validated in children with ataxia or acquired brain injury (Resch et al. 2020), and this would be of value to consider in future trials. This is particularly relevant in children with a cancer diagnosis where it is acknowledged that children can be isolated due to having less contact with their peers during prolonged treatment and have difficulty returning to previous levels of activity (Huang et al. 2011); therefore, exploring any change in participation is also important alongside any impairment level change in ataxia or balance.

It remains unclear if the outcome measures selected were sensitive enough to detect a change in the fairly short time frame of the study (due to low intervention numbers). However, the measures chosen have been used in other studies where a change has been shown over a number of weeks (e.g. Ilg et al. 2012, Schatton et al. 2017), and therefore do appear to have potential for measuring change. Their ease of use found in this study, also adds to their potential value.

The assessor therapists raised the only concern regarding the outcome measures with the choice of language of the PedsQL as presented earlier in the results. The development of the PedsQL included interviews with patients and their families in the initial phase prior to further development and testing and then further revision regarding relevance, understandability and reliability (Varni et al. 1998). It appears to have been extensively tested and reviewed prior to its adoption in general use. However, despite this, the literature reporting its development gives no indication about what informed the choice of terminology

within the statements. Concerns were raised quickly by the therapists (on behalf of participant 2) about the use of the word ‘cancer’, and a workable solution was put in place which all therapists agreed with. No further concerns were raised, but the issues raised with some of the terminology of the PedsQL should be highlighted if it is used in further clinical practice or trials.

The PedsQL was the outcome measure that was not completed on the most occasions. This was not related to the language in the questionnaire, but reasons recorded by the assessor therapist included, *“not completed due to the child’s understanding and attention”*, this is despite there being different versions adapted for individual age groups. These issues have not been reported in the literature previously. However, the PedsQL did lend itself to completion remotely where face-to-face assessments were not possible due to the implications of COVID-19.

The PEDI was also able to be completed remotely with no issues by parental questionnaire. However, the 9HPT was not able to be completed remotely due to the equipment required (a standardised peg board) which was obviously not available in the family home. The entire BARS was not able to be completed remotely due to the challenge of assessing eye movements without the therapist present. The SARA, although similar to the BARS, was able to be completed remotely; however, assistance from a parent/family member in terms of both positioning the camera and completing the finger chase item was required. The three items comprising the Bal-SARA are straightforward to assess via remote assessment providing space is available for the tandem walk assessment. Therefore, this subscale might be of value to use as a standalone measure, particularly if balance is the primary problem. Balance deficits in cerebellar ataxia are associated with difficulty in timing, planning and initiation of movement, increased body sway and lack of anticipatory postural adjustments (Winser et al. 2015), and it would be useful to see if the Bal-SARA is associated with sway in the paediatric population as has begun to be explored in adults (Bunn et al. 2015). Recently a development named the SARA-home has been described in the adult

population (Grobe-Einslir et al. 2021). This involves the use of a video-based tool to assess five items of the SARA in the home setting. Although promising to standardise the remote assessment of ataxia, it uses different items to the previously described Bal-SARA subset (and it is not the full item set) and therefore this makes comparison across studies difficult.

The Pediatric Balance Scale (PBS) could be completed by remote video assessment but required some preparation by the family, e.g. an accessible step and a parent to assist with changing the camera position. There is evidence that the adult version of the PBS (the Berg Balance Scale) is correlated with the SARA and Bal-SARA in adults (with MS) (Winser et al. 2015, Winser et al. 2018). This implies that the PBS is also of value for balance assessment in cerebellar ataxia in paediatrics and, although it has been used clinically, it has not been formally validated in children with PFT.

Implementing the option of remote video assessments as part of the study mirrored the rapid change in clinical practice as a result of the COVID-19 pandemic. A recent survey by the Association of Paediatric Chartered Physiotherapists (APCP) reported that 95% of respondents (472 therapists participated), had changed their use of technology as a result of the pandemic (APCP 2020). ‘Attend Anywhere’, the platform used in the study, was reported to be the third (after MS teams and Zoom) most commonly used option (out of 27 different platforms). It is noted that the majority of physiotherapists (76%) in the APCP survey felt that future service delivery would continue to include remote virtual options, therefore further identification of any specific barriers for remote video assessments in neurorehabilitation would be of value to explore (APCP 2020). However, from the exit interviews both parents who had the option of remote assessments felt that face-to-face assessments offered more for their child and were more productive.

Fatigue was identified as a theme in the embedded qualitative component (for the intervention group) and was raised as a challenge by more than one parent in the exit interviews. Therefore, recording this specifically as part of the assessments may have been

of value and the addition of a fatigue measure may be important in future studies. The choice of fatigue outcome measure is not clear cut. A systematic review by Crichton et al. (2015) identified 20 instruments with different qualities, although the authors highlight that the PedsQL MFS (multidimensional fatigue scale) is the most commonly used scale in research. The PedsQL MFS has been examined in childhood cancer and other chronic conditions such as rheumatology and diabetes (Daniel et al. 2013, Varni et al. 2004, Varni et al. 2009) and, therefore, may be an appropriate tool to consider for future studies.

8.14.2.3 Research design and protocol issues

A RCT design was selected for the feasibility study as the gold standard for informing a future RCT, however, research design inevitably impacts on recruitment. There did not appear to be any issues with the randomisation process as no participants were unwilling to be randomised, and only one parent expressed disappointment in not receiving the intervention. Thus, this acceptance was broadly supported by both the qualitative and quantitative findings. The other parents interviewed accepted that they knew not receiving the intervention was a potential option and part of the trial. These findings counter evidence reporting parent/participant preference for a specific type of treatment being a significant factor in participation in trials (Beasant et al. 2019).

Positive feedback was provided for children who were allocated to the usual care group that they found the ongoing monitoring reassuring in keeping with literature in other cancer trials (Nurgat et al. 2005). However, the frequency of intervention visits appeared to be an issue when declining the trial. Considering how significant recruitment issues were, alternative designs such as well controlled n=1 studies may be an option (Krasny-Pacini et al. 2018). However, this would potentially mean that the children would be in the study for a longer period (meaning additional time burden) even though a smaller number of children would be required to take part.

Another research design option is an active matched control, where any differences in presentation are not just related to additional hours of therapy input. It was discussed earlier in the chapter that the first step was to consider the intervention in comparison to usual care (acknowledging that usual care might be multidisciplinary). However, in the future, a matched active control group may be of benefit (e.g. low-tech substitute to VRT), in the context of a protocol that is set to an intensity level acceptable to the children and their parents. This would provide an understanding of whether the same results can be achieved using a low tech alternative. A low tech matched 'active control' was used in an adult stroke trial examining VR (Saposnik et al. 2016), the results noted no difference between the VR and low tech group, suggesting that type of task is less relevant as long as it is task specific and repetitive. This is in contrast to a pilot RCT study by Wang et al. (2018) in adults with Spinocerebellar ataxia (SCA) who reported an improvement in their VRT group (following four weeks of training with bespoke exergaming) which was not seen in the matched control group of conventional physiotherapy. Thus, they suggested that VRT may be superior to conventional therapy.

Block randomisation was chosen to ensure a balance between the two groups stratified according to age and ataxia severity. Although this approach aims to determine an even split over the whole target cohort, it does not necessarily ensure an even split at all times during the recruitment. This is demonstrated in the allocation to date (end February 2021) with ten children recruited, seven were allocated to usual care and only three to the intervention arm. Although with further recruitment this will balance, the analysis presented in this chapter was undertaken with an uneven split between the two groups.

It was noted on three occasions that assessors became unblinded to participant allocation. This was linked to the assessors and intervention therapists working within the same small department and appointments being conducted in the same vicinity. This does not appear to have been reported in other studies, however, practical issues such as these should be considered carefully to minimise such risks.

To increase family acceptability and potentially reduce concerns regarding travel burden, future protocols could be weighted to a higher home-based component. This would fit with the exit interview feedback from the parents in the intervention group. The option for the intervention to be weighted to home delivery was not part of the study design due the concerns previously reported regarding reduced compliance of home exercise programmes (Maring et al. 2013). Indeed, other studies have reported significant variance in home training (Ilg et al. 2012, Schatton et al. 2017), particularly reducing over time throughout the duration of the study (Baque et al. 2017). In this study the amount of home training completed by the 3 participants in the intervention group varied. The findings are not fully clear, due to incomplete participant diaries, but home training intensity was under the target set of three times a week for two out of the three participants (median twice a week). The literature also suggests that VRT with physiotherapy supervision is of increased benefit compared to no supervision (Hickman et al. 2017), therefore the study was set up to achieve a minimum threshold of physiotherapy supervised sessions which could possibly influence physical presentation, and then followed by home training to supplement the initial supervised sessions. This frequency was also supported by the PPI group in the planning stages of the study. However, due to COVID-19 and the rapid implementation of remote video appointments, the option of remote but supervised sessions may provide an alternative which is of benefit to the families, reducing travel time but also ensuring sufficient intensity of supervised practice to determine if VRT may be of benefit. This design would be similar to Sabel et al.'s (2016) study which used home based sessions that were remotely supervised for one session per week. Phase 4 has provided initial information about the feasibility of remote video assessment as part of a trial in the first instance and further exploration of remote video intervention sessions would be of value.

Despite low recruitment, drop out/withdrawal rate was low, with only one child withdrawing after assessment 2. The reasons for this child withdrawing were due to a combination of increasing other medical problems and fatigue; despite this their feedback regarding the

intervention was very positive. This is in keeping with reports that recruitment is typically more of a problem than retention in trials (Walters et al. 2017). One other child completed 2 out of 3 assessments (due to being unable to attend their second assessment), all other children completed all 3 assessments, indicating the feasibility of the design of the assessment process.

8.14.3 Feasibility of the intervention

Virtual training was chosen as the intervention due to the trend for its use in children with ataxia from different pathophysiological underpinnings (Ilg et al. 2012, Schatton et al. 2017) and the positive findings from the workshops. VRT also offered the opportunity of repetitive task/balance practice in keeping with principles of motor learning, this is supported by the e-survey where balance exercises were the intervention used most often by physiotherapists.

Only three children were allocated to the intervention group and therefore caution should be taken when interpreting these findings, however, all participants reported positive feedback regarding the VRT. The children confirmed that the gaming was enjoyable as observed in the results and parental feedback was also positive. This encouraging feedback is comparable to studies in other paediatric populations such as children with cerebral palsy (Brien & Sveistrup 2011) who reported that VRT is motivating and engaging. Although only three children were allocated to the training, the age range varied (5-14 years) and illustrated the potential for the training to be enjoyable and engaging across this age group. The children typically provided feedback that the most enjoyable game was the one they succeeded at, potentially highlighting the need to carefully consider game choice to provide a challenge without making it so difficult they cannot succeed and therefore lose motivation (Levac et al. 2015).

The VRT could be adapted to the children's differing functional levels as one child had more limb ataxia and another demonstrated higher level balance problems. No concerns were

expressed about utilising the gaming matrix by the intervention therapists. Minor challenges to using the technology were noted, e.g. difficulties *"for sensor to pick up at times"* were reported by both a therapist and a parent where it was difficult for a child to keep their limb still enough to register to start the games. However, all children were able to participate in full sessions when they attended on site for their hospital-based training sessions.

Positive feedback was also reported at both the end of week 1 and end of week 4 of the hospital-based training, although different experiences were reported, with one child reporting it became more difficult, possibly due to fatigue whereas another child reported it was easier. Fatigue was identified as a theme in both the intervention and exit group interviews for parents allocated to the intervention group. This has not been reported as a particular issue in studies examining ataxia previously but is a known problem in children who have undergone cancer treatment (Hockenberry-Eaton & Hinds 2000). Although in this study the intervention was able to be continued, fatigue seemed to be a particular issue when combined with the travel commitments. However, the families had taken this into account and used strategies to help accommodate this. One mother also expressed that they did not think their child could have coped with this level of training earlier following their surgery. This information again adds to the discussion of when to stage the intervention post-surgery. Typically, rehabilitation is more intense in the immediate post-operative period, however, the child is normally an inpatient at this time negating travel time (or potentially attending on site for treatment anyway) and therapy sessions may be shorter or less demanding in intensity according to the child's medical presentation. Recent information from an ongoing service development in Spain has observed that delaying rehabilitation to after 12 months post-operatively resulted in less improvement than children who commenced at 3 months post-operatively (Morales La Madrid 2020). Conversely Peri et al. (2019) report functional improvement in children on average 4 years post-operatively with enhanced therapy intervention. Therefore, timing following surgery remains under debate, but the intensity of training and ability to adapt therapy sessions according to the

child's presentation will be of particular importance if this is commenced earlier post-operatively. Monitoring of fatigue would also be of value as previously discussed and advice regarding pacing might be beneficial for families entering the intervention group. Fatigue was not raised as an issue by any families who were allocated to the usual care group.

Adherence to the hospital training component varied with children attending 7-10 sessions (median 7 sessions). Adherence has not always been reported in other similar trials that compare hospital/clinic-based adherence (e.g. Ilg et al. 2012, Schatton et al. 2017, Biffi et al. 2017). Piscione et al. (2017) report an 84% adherence in their community/group-based exercise study, and this compares with a median of 87% in this study. Despite fatigue being raised as an issue in the interviews it was not given as a reason for reduced adherence. Instead 'burden' of the study emerged and reasons for not being able to attend for 3 sessions a week centred around school and parental work commitments. Therefore, as previously discussed consideration of scheduling appointments and intensity of protocol remains key. In the future understanding if adherence is higher with remote supported VRT would be beneficial. Sabel et al. (2016) undertook a home-based supervised intervention reported that all 13 of their children participants with brain tumours completed the study. Although the frequency of the intervention sessions varied (from 38-69), the median number of sessions was 51, reaching the target intensity of five times a week over the ten-week intervention supporting this approach. Ongoing supervision by the physiotherapist does allow progression of the programme and monitoring of game selection. These factors are valuable for tailoring the programme and challenging the child to train at the appropriate level.

Despite positive feedback at the end of week 1 and week 4 hospital intervention visits, and expression of preference for a larger weighting towards home-based training, the amount of home training sessions varied. This is in keeping with Baque et al. (2017) who report varying levels of home training, typically under the recommended level targeted in the study (Baque et al. 2017). Barriers to home training included lack of space in the home

environment. Participation seemed to improve when the child completed the training with other family members e.g. one teenager did the training at home with their sibling, and another with their grandparents. This increased motivation with family members has similarly been reported in the literature as a way to increased engagement with home exercise programmes (Novak 2011), so suggesting strategies at the start of the trial to help sustain training might be useful. Strategies could include reward-based approaches, joint goal setting or recording training in a digital manner.

There were no significant technology problems raised from the therapists or families using the Xbox Kinect either in the home or clinic setting and the Xbox was familiar to the teenagers in the trial. However, it is noted that the Xbox Kinect is no longer manufactured and newer versions of the Xbox are not easily compatible with the Kinect. This highlights the difficulty of using technology in clinical trials which take a prolonged period to plan, undertake and report, by which point the technology is often outdated, obsolete or replaced by newer versions which may not be compatible. However, the principles of the virtual training can be carried forward in to planning of future research.

Overall VRT as a potential intervention met a number of constructs that have been deemed to contribute to acceptability (Sekhon et al. 2017).

8.14.4 Effectiveness of intervention

Whilst this study has provided early information about the feasibility of using VRT in children with PFT, it is not yet possible to determine any potential for effectiveness. This was not a primary aim of the study as it focused on feasibility. However, an objective was set to determine a sample size for a future trial. If the sample size target had been achieved it may have been possible to comment on any trends in the data and although this was not possible, some changes were noted.

Although there are some small changes in assessment scores for children in the usual care group, overall, there appears to be little change which is in keeping with the CARS study

(Hartley et al. 2020, submitted), where only a small amount of change is demonstrated over one year post surgery. Consideration of the trajectory of children in the usual care group would also be of interest in the future with a larger population to confirm this is in keeping with previous literature.

Despite not being able to determine any trends regarding effectiveness there are a number of considerations to take forward which could influence effectiveness and thus be relevant to future research. Key themes of intensity of intervention, whether the intervention was sufficiently focused in the context of children with PFT and the impact of COVID-19 are discussed further below.

This study included an intervention protocol consisting of 12 hours of hospital-based training (over 4 weeks) followed by 4 weeks of home training recommended to be matched at 12 hours. This intensity level is similar to Peri et al. (2019) who studied 11 children and young people (7-30 years of age) with ataxia secondary to ABI completing immersive virtual reality training who undertook 20 sessions (each 45 minutes duration) over one month (15 hours of training). This study is also in keeping with earlier studies as previously mentioned with similar protocols (Ilg et al. 2012, Schatton et al. 2017) who all suggested a benefit from VRT. This suggests that the proposed intensity is reasonable to achieve possible improvements but as noted in the literature review (Hartley et al. 2019) there remains wide variance in training 'dosage' reported in the literature with no clear consensus of the threshold required to influence physical improvement. Training duration also varies, with Baque et al. (2017) undertaking a 20-week study with 60 hours of training and, although observing positive results, participant feedback was that the frequency and duration of the study was too long to maintain. Thus, the balance of intensity to drive a clinical change over a sustainable period remains unclear. Further work in this area would be of assistance. A Cochrane review (stroke upper limb rehabilitation) suggested 15 hours of virtual training as a threshold to gain improvements (Laver et al. 2011, 2012, 2015), and having this information available to clinicians is of value to plan both research and guide rehabilitation

in the clinical setting. Schatton et al. (2017) noted that training intensity did correlate with clinical improvement, and therefore it is important to review any future results in the context of training fidelity. An example of this is illustrated in the presentation of the results, with the percentage of training intervention detailed between each stage of assessment; this may be important to consider in understanding any changes in scores in the future.

Another consideration was whether the intervention was focused enough to influence the specific difficulties a child with a PFT might present with. Off-the-shelf technology was chosen in part due to its more favourable feedback by the children. Also, it is available at a lower cost with increased accessibility and wider game variety, but it has less capacity to individualise task parameters and captures fewer performance metrics (Powell & Powell 2015). The VRT selected was not designed for a rehabilitation purpose and although it offers components relevant to motor learning e.g. repetitive practice, and the games chosen were considered with the population in mind, it still might not be focused enough to work on the specific difficulties children with PFT might present with, such as a combination of balance issues and limb ataxia or potential associated oculomotor problems. Previous research has not necessarily raised concerns regarding the use of off-the-shelf generic VRT; both e.g. Ilg et al. (2012) and Schatton et al. (2017) suggest a benefit in children with ataxia from a genetic origin with commercially available gaming. However, Winser et al. (2018) suggest that training needs to target the specific part of cerebellum involved, i.e. vestibulocerebelllum (to train gait and equilibrium) or spinocerebellum (proprioceptive or corticocerebellum (dual task training). In healthy adults, additional activation of the cerebellum during dual task training has been demonstrated (Wu et al. 2013), with the suggestion that combining a physical and cognitive task might result in improved outcomes. Some games might accomplish this dual element of training and therefore the importance of game choice is highlighted again. Lesion specific rehabilitation is a different focus to principles of motor learning which have previously been adopted as although motor learning may be limited in cerebellar ataxia there is some evidence that learning occurs with repeat

practice (Ioffe et al. 2006) and considering the type of feedback provided (Therrien et al. 2016). In terms of children with PFT and deep nuclei involvement, a dual task training approach could potentially be useful, but children may also have a vestibular component (due to the location of the vestibular nuclei in the floor and lateral walls of the 4th ventricle), therefore this lesion location specific approach to planning training might be more of a challenge in children with a large PFT with more widespread involvement. Clinically children with PFT do present with vestibular difficulties (potentially due to the output of the fastigial nuclei to the vestibular nuclei). However, the body of evidence in vestibular rehabilitation is in adults with peripheral vestibular problems or mild traumatic brain injury pathology (Kleffelgaard et al. 2019, Murray et al. 2017, Whitney et al. 2016). Vestibular exercises typically challenge visuo-vestibular mismatches (visual to head position conflict control), and some of this will be evident in VRT dependent on game choice, but in traditional vestibular exercises there is no reward or cognitive element so it is therefore unknown if traditional vestibular rehabilitation would be effective in children with PFT.

It should also be remembered that children with PFT may have also undergone adjuvant oncology treatment e.g. which might have also had an impact on their physical presentation. E.g., they could have peripheral involvement either from a vestibular apparatus or cranial nerve impairment or peripheral neuropathy from chemotherapy treatment, and as such children might have to adjust their learning strategy. If they have chemotherapy induced peripheral neuropathy they may not be able to use an ankle strategy to maintain balance (Horak et al. 1997), this highlights the need to consider in larger trials why some children may show more change than others. Consideration of baseline characteristics and initial INAS score may be of value in identifying particular issues which impact on the potential to improve with balance training, although this has not been done consistently to date in the literature, and Schatton et al. (2017) is one example of a study that has considered this approach.

It is also unclear if COVID-19 impacted on physical performance and subjective measures such as the PedsQL quality of life measure of children participating in the study. Whilst it is well reported that quality of life has been affected in the general population, the effect on the physical health for children with brain tumours is less well understood. However, with fewer opportunities to engage in physical activities and to access services this should be taken into consideration. The Teenage Cancer Trust reported that young teenagers with cancer were having more problems managing their physical health during the first wave of the pandemic with less support from physiotherapy (TCT 2020), and they highlighted the potential impact of this on their well-being. To acknowledge the potential impact of COVID-19, the timeline of when children were recruited is detailed in the results, although with small numbers it is difficult to interpret any impact. The embedded qualitative component did not explore this specifically, but one family highlighted (following the first wave) that they were familiar with this type of scenario as they had in effect adopted a similar 'shielding' process when their child was on oncology treatment so they felt they could cope with the COVID-19 restrictions without too much difficulty.

It should also be considered if there is potential for the influence of the Hawthorne effect (i.e. a potential impact on the participants' behaviour/responses as a consequence of being part of the study, and not due to the effect of the intervention itself, (McCambridge et al 2014)). This should be acknowledged when considering the full results when the study is completed. The Hawthorne effect may also be apparent in the feedback from the usual care group who reported a reassuring benefit of being monitored as part of the trial, raising the possibility that the usual care group itself has some limitations and may not be reflective of typical usual care conditions.

Overall whilst VRT appears to have potential for children with PFT, no conclusions can be made to date regarding the effectiveness of the intervention. The specific intensity of training, game choice and focus of rehabilitation task remains an area for future research.

8.14.5 Impact of COVID-19

Guidance on COVID-19 was issued on 16th March 2020 and at that time the ASPECT study (Phase 4) was open to recruitment across three sites. The study was categorised as a Level 2 (mid priority study) by the sponsor site and therefore was suspended to recruitment across all sites from this date. The NIHR, local Clinical Research Network (CRN) and all other sites were informed of this development. A risk assessment was undertaken with the supervisory team to identify study specific factors in relation to participants (e.g. impact on recruitment, impact on children already entered into the study), steps for reopening, and to consider wider issues of financial and time implications on the fellowship. This risk assessment was updated monthly throughout the first wave of COVID-19 (Appendix 55). At the time when the study was suspended no participants were undertaking the intervention 'arm' of the study, although two participants were active in the trial in the usual care 'arm'. Therefore, these participants were contacted over the telephone to explain the situation. During telephone contact the outcome measures that could be completed by telephone (PEDI-m, PedsQL and subjective impact) were undertaken.

In order to accommodate an expected prolonged change in working practices in response to COVID-19 an amendment to REC and HRA was submitted in May 2020 to request approval for the option of remote video assessments on reopening of the study. This amendment (which was subsequently approved in July 2020) enabled a reduction of visits to the hospital for children and also minimised flow of traffic through each site. 'Attend Anywhere' was chosen as the platform for the remote video assessments as this was approved by the NHS and was being used successfully at a number of hospitals for routine practice during the COVID-19 pandemic including at the host site. Considerations of the use of virtual assessment was informed by guidance produced nationally by the Chartered Society of Physiotherapy (2020) on remote physiotherapy delivery options (https://www.csp.org.uk/news/coronavirus/remote-service-delivery-options) taking into

account factors such as choice of digital platform, practicalities of IT technical issues, steps to prepare patients and tips for a successful virtual consultation.

When routine practice began to resume at hospital sites, a request to reopen the study was made to the Sponsor Oversight Committee (SOC) at the host site. Guidance from the NIHR was followed with consideration of study viability, safety, capacity and site readiness and prioritisation. Evidence of this is detailed in Appendix 56. The host site reopened Phase 4 RCT on 22nd July 2020. Subsequently all other sites were required to go through local reopening procedures. However, there were significant delays in reopening other sites. Site 2 is still awaiting local approval (April 2021) but Site 3 reopened in February 2021. Site 4 opened in September 2020 but due to redeployment of the physiotherapists with the second wave of the pandemic recruitment was not possible.

Due to ongoing restrictions with the second wave of COVID-19 (including 'local lockdown', restricted travel and restrictions on patient flow in hospitals) and with consideration of reduced completion of hospital-based intervention sessions by participants to date, a further amendment was submitted in November 2020 (approved in January 2021) to request the option of remote video intervention sessions. A minimum of the first two sessions were required to be conducted on the hospital site to ensure that the participant was familiar with the equipment and training programme. Following this, if the intervention therapist deemed it was safe to do so, the participant could take the equipment home and any further appointments in the hospital-based intervention block could be completed remotely if the child was not able to attend on site. The second home-based intervention block remained unsupervised as originally planned.

Reopening and site visit procedures were also informed by regularly updated COVID-19 related guidance from the Children's Cancer and Leukaemia Group (CCLG) (https://www.cclg.org.uk/news/coronavirus-covid-19-guidance-for-children-and-young-people-with-cancer-undergoing-treatment). Updated guidance by the CCLG published on

31st July 2020 reported a low number of children managed by all CCLG centres throughout the UK testing positive for COVID-19 with children typically presenting with mild symptoms. CCLG guidance provided recommendations for three groups of children:

- Highly vulnerable children; currently undergoing chemotherapy treatment for ALL/AML/lymphoma or following stem cell transplant (until immune system has recovered);
- Vulnerable children; currently undergoing chemotherapy for any other cancer and up to 6 months following completion of completion, are on long term maintenance steroids, have completed treatment for cancer but have ongoing chronic lung, heart, kidney or neurological conditions, receiving targeted/antibody cancer treatment; and
- Not vulnerable (i.e. same risk as healthy children); over 6 months following completion of treatment.

No children deemed highly vulnerable were eligible for the RCT feasibility trial. Children who had received surgical intervention only or had completed chemotherapy more than 6 months previously, who were the predominant population for this trial were not classed as vulnerable and were the first phase of children identified as potential participants. Children between 0-6 months post completion of chemotherapy treatment were considered in the second phase of reopening in discussion with their oncology team. It was noted that children classed as vulnerable were still advised they could attend school whilst following social distancing and hand hygiene advice.

Site visits by children and their parents for the study were, wherever possible, tied in with routine clinic appointments to minimise the number of visits required, and all visits (assessments and intervention) were conducted according to local standard operating procedures with regard to personal protective equipment and cleaning procedures.

A request for a 6-month extension to the overall programme of work was made to the NIHR in August 2020 in view of the impact of COVID-19 on Phase 4, alongside a further

substantial ethical amendment request to extend the initially proposed end of recruitment date from 31st December 2020 to 31st December 2021.

During the second wave of the pandemic (Winter 2020 into 2021) the study remained open to recruitment. However, increased clinical demands on allied health professionals across sites impacted time available to be spent on the study (by other PI's and assessor/intervention therapists). Remote video assessments and intervention sessions, where relevant, were offered to families considering taking part in the study during this time period. The study risk assessment was reopened and regularly reviewed by the supervisory team. Parents of the two children recruited following the study reopening both expressed a preference for face-to-face appointments. They felt their children got more out of these sessions and the sessions would be more productive. Therefore, despite potential advantages of eliminating travel time and concerns of attending a hospital based during the pandemic, the families valued direct contact with the physiotherapist. As stated previously it would be of benefit to explore remote assessment further to determine its acceptability and accuracy.

8.14.6 Limitations

Strengths of Phase 4 are presented later in the thesis in Chapter 9. The main limitations of Phase 4 of the study relate to small sample size. This was influenced by three factors; a smaller than expected number of children being eligible for the study, low recruitment rate, and the suspension of the study due to COVID-19. Recruitment rate has been extensively discussed above, and engagement of other centres to recruit to the study and delays in local approvals have been highlighted as a key factor. The small sample size means it is difficult to draw any firm conclusions from the data, however, preliminary data has been provided in an area that has not been explored before and the embedded qualitative component adds strength to the findings.

It is also noted that for the three children who were allocated to the intervention arm, none completed the full planned 12 hospital-based intervention visits. The reasons for this have been discussed previously, and although this is a limitation, as the primary purpose of the study was feasibility including that of the intervention protocol, this lower adherence rate does provide information that can be used in planning of subsequent trials.

The trial also included one remote video assessment. In the context of a feasibility trial this did not cause major problems, but a larger study considering effectiveness would need to ensure that remote assessments are of equivalent value to face-to-face assessments, (or that there was a similar mix of remote assessments in each group) to ensure the results were not influenced by change in assessment practice.

Phase 4 used a range of outcome measures to encompass ataxia, balance, functional ability and quality of life. Limitations of individual measures have been presented earlier, and it its acknowledged that no single measure is seen as gold standard in children with PFT. However, the selection of measures was informed by previous research and clinical practice, and positive findings regarding their acceptability and use in this study have been observed.

Additionally, the study would have benefitted from a more defined stop/go criteria to assist with overall assessment of feasibility and evaluation of potential for progression. This could have been determined through collaboration with the research team, assessors and PPI group and been determined prior to the commencement of recruitment similar to that presented by Young et al. (2019).

8.14.7 Dissemination

Individual feedback of assessment results was provided in writing based on parents' request following their child's completion of the study (or at time of withdrawal as appropriate). This was shared with the community physiotherapists involved with the child, where appropriate,

if the parent requested this. A summary of the study is planned for the North West Neurosciences Network website for further review by families and professionals.

The protocol of the trial was summarised and presented as a poster at the BPNA Neuro Oncology Study Day in March 2020. The study is planned to be submitted for publication later in 2021.

8.14.8 Future research recommendations

Phase 4 has provided preliminary information about the feasibility of conducting a RCT in children with ataxia following surgical resection of PFT. Currently due to incomplete data with a low number of children recruited to date, the recommendations presented in this chapter take this into account. As noted earlier, Phase 4 remains open to recruitment (via ethics approval and NIHR extension as discussed above) with planned closure in December 2021. Ongoing recruitment aims to add weight to the interim data and any final feasibility recommendations will be made in the light of the next six months of data.

The use of emerging literature regarding stop/go criteria (Young et al. 2019, Mbuagbaw et al. 2019) and assessment of feasibility including an acceptability framework (Sekhon et al. 2017) may be of value to consider when reporting the full feasibility trial data.

A large well controlled trial may be of value in the future to determine the effectiveness of the physiotherapy intervention (following confirmation of sample size estimate). However, further work is required to determine optimum timing and intensity of physiotherapy, including the mix of home and hospital-based training to ensure that future protocols have the potential to optimise outcome whilst being acceptable to children and their families.

Further exploration of the value of remote assessments (with subsequent validation specific to this context) and remote intervention is also of interest in this population as this area of practice has developed rapidly with COVID-19 and offers benefits in terms of reduced travel time for families.

Although no clear recommendations regarding the use of VRT can be incorporated immediately into clinical practice, Phase 4 has provided insights into the use of a set of outcome measures, including those that can be completed both remotely and face-to-face.

Whilst Phase 4 has focused on specific elements of feasibility (e.g. feasibility of RCT design, feasibility of intervention with a focus on acceptability, practicality and adherence), Bowen et al. (2009) suggest that in addition to acceptability and practicality other areas such as adaptation, expansion, demand and integration should also be considered when considering the feasibility of a rehabilitation intervention highlighting further potential areas of research.

8.15 Conclusion

In conclusion, Phase 4 has provided preliminary information on the feasibility of conducting a RCT examining VRT in children with ataxia following surgical resection of PFT. Specific objectives of exploring process, intervention and outcome measures have been achieved and supported by insights from children and their parents within the embedded qualitative component. Ongoing recruitment aims to confirm final feasibility recommendations.

Further examination of timing and intensity of intervention and optimisation of recruitment is required prior to planning a larger scale multi centre RCT.

Chapter 9 Discussion

9.1 Introduction

Physiotherapy is considered to be critically important for children with ataxia, including children recovering from posterior fossa tumour (PFT) (NICE 2005). However, studies to date offer inadequate guidance about the feasibility and effectiveness of interventions, the timing of the delivery of interventions, and the selection of valid and reliable outcome measures for this population group (Hartley et al. 2019).

The programme of research reported in this thesis therefore aimed to:

- Identify valid, reliable and responsive tools to measure the severity of ataxia in children with PFT in the acute phase and over the long-term (Phase 1);
- Understand the range and scope of contemporary physiotherapy interventions, outcome measurement and the specific difficulties physiotherapists face when working with children with PFT (Phases 2 and 4);
- Understand the views of children and their parents concerning feasibility and acceptability of virtual reality training programmes (Phases 3 and 4); and
- Determine the feasibility of conducting a randomised controlled trial examining the effectiveness of virtual training on ataxia in children following surgical resection of a PFT (Phase 4).

In this chapter the original contribution to knowledge is presented. The results of each investigation are then discussed in relation to the research questions and previous research in the field. The strengths and limitations of the studies are discussed. The implications for physiotherapy practice and further research are reported, and the outputs from the programme of research are presented.

9.2 Original contributions to knowledge

This study (Phases 1, 2 and 4) has made four key original contributions to knowledge.

1. **Identification of gaps in the evidence-base:** The literature search (Hartley et al. 2019, Appendix 3) highlighted a lack of consistency in assessing ataxia severity and demonstrated the absence of high-quality evidence to guide physiotherapy practice for children with ataxia. This study has addressed a gap in the literature regarding physiotherapy assessment and management of children with ataxia following surgical resection of PFT.
2. **Contributions related to assessment outcome measures**: This study has provided a new understanding of ataxia outcome measures that will allow clinicians to determine if the severity of ataxia has changed in children with PFT following surgery or rehabilitation. New information has been presented on the SARA and BARS and the study identified a preliminary minimally clinically important difference (MCID), strengthening the case for using the SARA scale both in clinical practice and in research (Hartley et al. CARS paper submitted 2020, Appendix 57). The potential risk factors for severity of ataxia in terms of tumour location and tumour histology were explored (Hartley et al. 2018, and Hartley et al. CARS paper submitted 2020), highlighting that children with medulloblastoma and midline tumours demonstrate more severe ataxia than those with low grade glioma and unilateral tumours. The study also demonstrated the feasibility of using the SARA pre-operatively and revealed for the first time, initial information on the course of ataxia in children following surgery up to three years following surgery. This has led to work reported in a paper which discussed changes from pre-operative baseline to early and late post-operative ataxia scores (Hartley et al. CARS paper submitted 2020, Appendix 57).

3. **Contributions to mapping current physiotherapy practice:** This is the first study to identify current international physiotherapy practice for children with ataxia following surgical resection of PFT. It has revealed the wide range and inconsistency between therapy treatment interventions used by physiotherapists and highlighted consensus in terms of treatment intensity (Hartley et al. 2020, Appendix 12). It has also provided preliminary information on clinicians' perspectives about the challenges to rehabilitation noting that these result from a combination of child and family factors, condition-specific factors and physiotherapy delivery factors. The knowledge generated about current practice by experts in the field is important in an area where there is a lack of literature. This information contributes to the evidence-base for planning future clinically meaningful research.
4. **Contributions to knowledge about the feasibility of conducting an RCT using VRT in children with PFT:** This study has provided preliminary information regarding the feasibility of conducting an RCT in children with PFT. Feasibility regarding assessment and outcome measures has been demonstrated although adaptations to recruitment strategies are likely to be needed. Preliminary findings also demonstrate that VRT may potentially be used as part of a physiotherapy programme for children with posterior fossa tumours with no serious adverse events observed. Non immersive virtual training for children with ataxia following PFT has only been previously reported in individual case study reports. Phase 4 supports the findings of previous research which used VRT predominantly in children with cerebral palsy, highlighting that VRT is potentially an option in other areas of paediatric practice. Phase 4 has shown that VRT for children with PFT can be carried out in the hospital and home setting. By using a mixed methods approach in Phase 4 this study contributes new knowledge and advances the field as research designs engaging children and parents are not commonly used in paediatric neurorehabilitation. The knowledge gained from child and parents' insights can also assist in future planning of rehabilitation protocols.

All these original findings have provided information that can readily influence practice and inform the development of future trials and clinical guidelines.

9.3 Synthesis and discussion of results with respect to the research questions

In this section the key findings and discussion points from Chapters 5, 6, 7 and 8 are brought together to provide a synthesis and overview of the learning and contribution to knowledge in relation to the specific research questions of the programme of research.

9.3.1 Research Question 1: What are the most appropriate scales to measure ataxia severity in children with posterior fossa tumours?

This programme of research demonstrated that the SARA (Schmitz-Hubsch et al. 2006) is feasible and quick to use with children with PFT in the pre- and post-operative setting. The SARA detected subtle changes in ataxia severity in this population. This degree of sensitivity indicates that the SARA may be the most appropriate scale to use for children with PFT. The Bal-SARA subscale (Bunn et al. 2015) may be particularly useful to measure the impact of training interventions in young children with PFT. Further research is required to fully evaluate the potential of the Bal-SARA, but findings from this study show the SARA can be used with confidence by clinicians working with children with PFT to monitor ataxia severity. It offers several advantages over the BARS (Schmahmann et al. 2009), including the availability of normative values in healthy children (age 4-16 years) (Lawerman et al. 2017a) whereas this is not available for the BARS. The availability of normative values is of particular importance when using the scales in longitudinal trials e.g. such as Phase 4, as these values can inform analysis to ensure that change is due to the impact of an intervention and not due to age related changes. Normative values are particularly important in paediatrics as both the SARA and BARS are known to be age dependent in healthy children (Brandsma et al. 2014) and this has been confirmed for the SARA in children with

PFT (Panzeri et al. 2020). Further benefits of the use of the SARA along with the new knowledge brought by Phase 1 are presented below.

Both the SARA and BARS are feasible, reliable, valid, and quick to complete based on the standard examination of coordination in children with PFT (established by the original CARS study and further supported by Phase 1) (Hartley et al. 2015). Additionally, Phase 1 findings demonstrated that both scales were responsive to change over time in children with PFT which is a new finding as this has not been examined before. The SARA appeared to identify subtle changes that were also perceived by clinicians, but which were not picked up by the BARS, potentially because the BARS has limited items looking at midline and balance issues. The finding that the SARA is more sensitive than the BARS, may be important in practice to detect a change due to intervention or equally to identify any early clinical deterioration (e.g. in the case of relapse). The literature examining the SARA and BARS scales in adults demonstrates consensus in that both scales are reliable and quick to undertake (Schmitz-Hubsch et al. 2006, Schmahmann et al. 2009, Yabe et al. 2008), though the floor and ceiling effects of both scales are not widely reported. Longitudinal examination to consider responsiveness in adults has only been examined for the SARA (Schmitz-Hubsch et al. 2010); this adds to the confidence about the use of SARA, whereas uncertainty remains for the BARS.

A minimally clinically important difference (MCID) of +/-2 is suggested (for both the SARA and BARS) from the results of this study and, although this would benefit from further confirmation with a larger data set, it does align with other literature. A threshold of two (or more) was also suggested by Lawerman et al. (2017a) to allow for inter-individual variability in maturation following analysis of normative data in healthy children, thus corroborating the data in this study. A MCID of 1.1 for the SARA was suggested in adults (Schmitz-Hubsch et al. 2010) and, in view of increased variability in performance of children, a slightly higher MCID for children does appear appropriate. Therefore, the suggested MCID of +/-2 was

able to inform Phase 4 of this study. This was possible as Phase 4 was conducted over a short time period and not designed to explore long term training effects. In Phase 1 the focus of analysis was a change in ataxia perceived by the clinician, future research should also consider what is meaningful change to the child and their parent.

The findings show that both scales respond differently according to tumour type and location, suggesting that children with medulloblastoma and midline tumours demonstrated increased severity of ataxia. This is the first time this has been demonstrated for the SARA and BARS and adds weight to the use of the scales both in clinical practice and in research. Although Robertson et al. (2006) suggested that children with medulloblastoma associate with a higher ataxia severity at one month post-operatively, this is the first time ataxia severity has been reported longitudinally beyond one year post surgery with the use of standardised outcome measures in children with PFT. The longitudinal nature of this study is an important factor as both Konczak et al. (2005) and Kuper et al. (2013) describe damage to the deep cerebellar nuclei as being a risk factor for long term ataxia. More recent information based on a cross-sectional study in 19 children (1-7 seven years post diagnosis) demonstrated that increased ataxia was associated with reduced integrity (volume loss) of the cerebello-thalamo-cerebral pathway, particularly in those with medulloblastoma (Eun Oh et al. 2017). Future studies would benefit from closer examination of the influence of tumour location potentially in association with detailed longitudinal analysis of MRI findings.

This study adds knowledge regarding medulloblastoma and midline tumours as risk factors of more severe ataxia, which should be confirmed with a larger data set and more detailed examination of tumour location and histology (e.g. molecular subgrouping). In Phase 1, a larger gap in the longitudinal course of ataxia was observed with tumour type comparison (medulloblastoma compared with low grade glioma) rather than with tumour location (midline compared with unilateral). This indicates a larger effect on ataxia by tumour type. This is despite the tendency for medulloblastomas to be midline in location. This suggests

that tumour location is not the only explanation for increased ataxia, and the influence of adjuvant treatment (e.g., chemotherapy and radiotherapy) should be considered. This has only been partially explored in the literature to date. However, although previous studies have suggested that children with medulloblastoma have significant ataxia (Bull et al. 2007, Robertson et al. 2006), these studies do not present comparison of physical difficulties with other tumour histologies. Piscione et al.'s (2014) study included a similar number of participants (n=30) to this study and considered the influence of adjuvant treatment. They reported that chemotherapy (but not radiotherapy) affected strength and agility thus contributing to lower long-term physical functioning, which would be in keeping with findings from Phase 1 of this study. This potentially indicates the need to be aware of sensory ataxia in addition to cerebellar impairment. However, to confirm findings from this study and Piscione et al.'s (2014) study and to be able to determine the particular influence of adjuvant treatment compared with location, a larger dataset would be of value as this would allow multivariate analysis to determine whether tumour location, histology (including molecular sub-type) or adjuvant treatment have the most impact on ataxia. An online database accessible to therapists could provide an option to gather information from clinical practice from across multiple centres and this model is already in place for other conditions e.g. the CPIP (cerebral palsy integrated pathway) database for children with cerebral palsy. Therapists could then use this information to anticipate therapy needs and assist with caseload planning. Examination of other potential associations of ataxia with commonly seen problems such as audiovestibular dysfunction or executive function problems would also be of interest to identify children who might have a more severe course of ataxia and those who have potential to change with rehabilitation in cases where the underlying risk factor can be influenced by treatment e.g. vestibular dysfunction.

In addition to examination of the ataxia scales, ataxia severity was tracked longitudinally to understand the natural history of ataxia in children with PFT, and also to determine whether physiotherapy interventions could be targeted at specific post-operative recovery phases.

Phase 1 highlighted an initial improvement in ataxia in the first three months post-operatively which is in keeping with other literature reporting recovery in the wider acquired brain injury field (Kelly et al. 2014). However, one year post-operatively, persistent ataxia with minimal change was evident. The course of ataxia, with slowing of change after 1 year post-operatively also highlights potential windows of opportunity for rehabilitation. This points to the importance of rehabilitation in the acute stage where children have the potential to show significant gains, but also demonstrates that more intensive input may be required to influence a change later post-operatively.

It remains unclear whether there is a different mechanism of recovery in the first few months post neurological insult to that which might occur later. The persistence of ataxia is supported by studies which report long term ataxia and balance problems in children with brain tumours (Piscione et al. 2014, Sonderkaeer et al. 2003). Collectively this information can be used to counsel families regarding the potential long-term risk of ataxia, to explain the likelihood of the need for long term rehabilitation and provide honest communication about physical problems their child might present with. Additionally, further examination of specific trajectories dependent on initial severity of ataxia (e.g. mapping change according to mild, moderate and severe ataxia at baseline assessment) would further assist with providing families with evidence-based information about future recovery potential. These trajectories were not able to be examined in Phase 1 due to small numbers in each subgroup.

The option of using the Bal-SARA was also identified in the feasibility RCT (Phase 4). This is useful because limb coordination can be difficult to measure in children under the age of 5 years. The Bal-SARA appears to have favourable properties as a sub-scale of the SARA and could potentially track change through time in young children with PFT. Formal examination of the Bal-SARA was initially completed in adults (Bunn et al. 2015, Winser et al. 2017), and its reliability and validity has been reported in children with early onset genetic

ataxia (Lawerman et al. 2017b). The ability to use sub-scales of the SARA provides further options for practice, however, further validation of the Bal-SARA to examine its responsiveness would be of value in children with acquired ataxia. Another favourable property of the Bal-SARA is the finding that it is amenable to remote video assessment. Considerations of remote assessment are discussed further in section 9.3.3 in the context of the feasibility RCT.

Phase 2 of the study identified that 75% of the physiotherapists who participated in the survey used standardised outcome measures in their practice and the SARA scale was the most commonly used outcome measure in this population (by 28 physiotherapists), indicating its relatively widespread use in clinical practice. These findings add value to advocating the use of the SARA as it is widely known about by clinicians across different countries and is already the clinically preferred scale (Panzeri et al. 2020). The results of this study can enhance clinicians' confidence that they are using the most widely accepted outcome measure to determine severity of ataxia.

A complete data set (no missing values) was recorded for the SARA and the BARS during 23 out of 24 face to face assessments in the feasibility RCT (phase 4) which provides preliminary support for the feasibility of these measures for clinical practice and research. The strengths of the SARA, evident in Phase 4, in terms of the short time it takes to use this scale and its familiarity to clinicians is likely to underpin its utility in future research and clinical practice.

The findings of Phases 1, 2 and 4 of this study demonstrate that the SARA scale is appropriate to use in children with ataxia following surgical resection of PFT. However, the SARA scale assesses severity of ataxia based at an impairment level, in terms of issues with body structure and function (ICF framework, WHO 2001). Although, as previously discussed, this is of value to clinicians as a tool that can be used quickly in the acute stages from pre-operative assessment and then repeated at multiple post-operative stages, it is

clear from the findings of this study that other outcome measures should also be considered. Other authors have noted that outcome measures such as the SARA do not assess change meaningful to the child and family (Galvin et al. 2010) and findings from this study support the call for this to be prioritised. This study has demonstrated the value of parent-centredness within research of this nature with strong PPI and engagement throughout the phases, and further involvement in any future planning is of importance. Despite the detailed consideration of SARA in this study, it is clear that shifting emphasis from solely clinician-oriented to participation level measures and patient-reported outcome measures is likely to be of benefit, particularly later in the child's journey when the focus has moved away from impairment to measures of reintegration in family life, leisure activities and school. This proposed shift aligns with Morris et al. (2015) who recognised that to be meaningful, outcome measures should be valued by patients and carers, be consistent with what clinicians are aiming to measure, and be robust in terms of measurement properties. However, no single outcome measure typically achieves all of these properties, therefore a core set of outcome measures for children with PFT may be beneficial. Indeed, core sets of outcome measures are now being developed in various paediatric healthcare populations such as e.g. neonatal development research (Webbe et al. 2020) and childhood epilepsy (Crudgington et al. 2019). This study provides evidence of the strength of the SARA and proposes that it could be adopted as part of a core set of outcome measures alongside activity and participation measures which are discussed further below.

In summary, this study has added new information on the use of the SARA and BARS in children with PFT, highlighting the advantages of the use of the SARA. In further clinical trials it would not be necessary to use both the SARA and the BARS to assess ataxia.

The key findings related to Research Question 1 are:

- Both SARA and BARS are feasible to use for children with PFT (aged 4-18 years);

- The SARA offers four key advantages; detection of subtle changes in ataxia, option of use of the subscale Bal-SARA, availability of normative values, increased awareness by clinicians; and
- Increased severity of ataxia is observed in children with medulloblastoma and midline tumours.

9.3.2 Research Question 2: What is the range and scope of current physiotherapy interventions, outcome measurement and the specific challenges physiotherapists face in working with children with PFT?

A large range of treatment interventions and outcome measures are used in clinical practice for children with ataxia following PFT management and these are collectively presented for the first time in Phase 2 of this study (Hartley et al. 2020, Appendix 12). Although a wide variety of treatment interventions and outcome measures to manage children with ataxia from any origin are presented in the literature, these are predominantly related to ataxia from other causes (e.g. genetic pathologies) (Hartley et al. 2019, Appendix 3). Enhanced therapy intervention for children specifically with ataxia following PFT surgery (or within the wider acquired/traumatic brain injury field) has not previously been well reported as highlighted in the literature review. Of the 11 main studies examined in the literature review, involving 21 children in total (Chapter 3), only three (two single case reports, and one case series (n=3)) included children with ataxia from a non-genetic cause (i.e. tumour, haemorrhage or trauma) and these varied in time post insult from five months to 3.5 years. A non-randomised pilot study by Peri et al. (2019), published after the completion of the initial literature review, examined therapy intervention, in this case immersive virtual training in children, young people and adults (7-30 years of age) affected by ataxia secondary to acquired brain injury (with 9 out of the 11 participants having a tumour diagnosis). Peri et al.'s (2019) study provides initial information on the potential use of virtual training in this population but, focuses on immersive training which is not necessarily widely available and

not typically able to be used in the home setting. Although Phases 3 and 4 of this study add to the evidence base with regards to the use of non-immersive virtual reality training including a home training component, overall, there remains a lack of high-quality evidence from large or well controlled trials. This lack of both good evidence and consensus regarding management was one of the key challenges raised by physiotherapists in Phase 2 of the study, with physiotherapists highlighting the need for clinical guidelines and further research for children with PFT.

Further challenges to rehabilitation raised by physiotherapists in Phase 2 of this study related to child and family factors and condition-specific factors. In terms of child and family factors, expectations from physiotherapy and engagement with physiotherapy, alongside psychosocial issues were raised. However, this was mainly from an acute (early recovery phase after surgery) rehabilitation perspective, with physiotherapists noting it was difficult for children and families to engage in rehabilitation when they might be undergoing adjuvant oncology treatment. During this acute rehabilitation period, parents can often have reservations about integrating therapy into the child's programme when they were seen as unwell. These findings resonate with work by Walker et al. (2014) who described families' feelings of helplessness and loss of control following surgery, describing two case studies of children requiring intensive acute rehabilitation input following a diagnosis of cerebellar mutism syndrome. Wibroe et al. (2020) also reported similar findings informed directly from childhood survivors of cerebellar mutism syndrome who observed that they felt like that they had been wrapped in cotton wool, even after the acute phase of recovery, with a lack of autonomy and independence.

Fatigue was raised as a condition specific factor by physiotherapists in Phase 2 of the study and also emerged as a challenge during Phase 4 of the study. Two participants and their parents reported the training in addition to travel time had a negative impact on fatigue. The families attempted to adopt their own strategies to deal with this, including pacing other

activities, but it remained a discussion point raised by the parents in the exit interviews. This finding is supported by Wibroe et al.'s (2020) qualitative study which again notes fatigue as a repeated issue for young adult survivors of childhood brain tumour. It might be therefore of value to have a specific fatigue-related measure as one of the core outcome measures in future studies.

The inclusion criterion for participants in Phase 4 of this study of 1 to 3 years post-surgery was informed, in part, by the e-survey, as this timing allowed the completion of any adjuvant treatment before the child's participation in the study. This aimed to negate any difficulties of balancing rehabilitation with chemotherapy which was raised as a challenge by physiotherapists in Phase 2. This also allowed enhanced therapy intervention to be targeted when recovery typically begins to slow, one year post-operatively, as indicated by findings from Phase 1 of this study. The criterion aimed to minimise the chance that any post-operative change would have occurred naturally. This is in keeping with the Peri et al. (2019) study where participants were on average 4 years post-diagnosis, which is quite a long time after the initial surgery. However, recruitment was a challenge for Phase 4 of the study as discussed in Chapter 8, and although chosen to coincide with completion of treatment and the natural slowing of improvement, reasons for not participating included concerns regarding missing school, and parents now wanting their child's focus to be on education rather than rehabilitation. These findings may raise the idea of shifting the setting of the research fully into the community and home setting. One family also reported they felt they had tried all different types of rehabilitation and just wanted to move on towards a 'normal life'. Conversely, a family who did participate reported they felt one of the benefits of taking part was they had further monitoring when other services were withdrawing as they were further post-surgery (over 12 months), and they found this reassuring. Contrasting the evidence from Peri et al.'s (2019) study, a recent rehabilitation service development in Spain for children with brain tumours presented at ISPNO 2020 (Morales La Madrid 2020, unpublished proceedings) observed that delaying rehabilitation to after 12 months post-

operatively resulted in poorer outcomes compared to those children who had a rehabilitation programme commenced at 3 months post-operatively.

Therefore, despite the rationale for the timing of the intervention, it remains a difficult balance to ensure the child and family have time following surgery and any treatment to focus on physical rehabilitation but not delaying too long where priorities of rehabilitation have changed again. Potentially if rehabilitation is part of a clearly planned overall treatment package scheduled at a certain time point it may be seen as a natural part of treatment rather than an optional extra. Other forms of rehabilitation might include social rehabilitation and educational rehabilitation which have been highlighted as key to children with PFT who have gone through the rehabilitation process (Wibroe et al. 2020). Although not necessarily exclusive to physical rehabilitation, understanding the goals of the children and their parents at any specific time point may be key to successful rehabilitation. Overall, this study combined with the literature demonstrates that it is possible to offer enhanced intervention from 3 months post-surgery up to 4 years post diagnosis. However, the optimum timing of therapy intervention requires further research and confirmation to ensure the best outcome and engagement.

Findings from Phase 2 demonstrated that although a range of interventions were used in clinical practice, physiotherapists were attempting to use virtual training as one of their treatment options, supporting its use. However, physiotherapists in Phase 2 perceived that resource issues and condition-specific issues were challenges to using virtual training with children with PFT. Condition-specific issues were particularly related to the use of virtual training in the acute setting where therapists reported the focus was more on functional assessment and tasks to facilitate discharge with not enough time to introduce virtual training. This is supported by one of the standards for neurosurgical units which is length of stay for children following surgery for a brain tumour, with the aim for admissions to be under one week (NHS Specialised Services 2012). However, Hamari et al. (2019) report

that off-the-shelf virtual training (Nintendo Wii) can be incorporated into an inpatient setting, using this with 36 children with a non-CNS cancer diagnosis (e.g. leukaemia) albeit for a different aim which was to encourage ongoing activity during an inpatient stay for oncology treatment.

Considering barriers to virtual training, physiotherapists (Phase 2) raised concerns that children might be frustrated if they could not do an activity that they had previously been able to do, although this was not evident in any of the feedback from children or parents in Phases 3 or 4 of the study. However, Phase 4 findings did show that children reported highest enjoyment of games they scored the best on, indicating that game choice could be important to maintain motivation. This is supported in the literature on VRT in other paediatric populations (Levac & Miller 2013, Levac 2016).

In summary, rehabilitation in children with brain tumours presents unique issues compared to rehabilitation for children with other causes of acquired brain injury. This is because the specific tumour diagnosis may require adjuvant treatment, surgery might just be the first step in their management, and further treatment might also have potential physical and cognitive consequences (Sonderkaer et al. 2003). For the first time in this population group, Phase 2 of this study reported physiotherapist perceived challenges of rehabilitation; further exploration of parent and child perceived challenges would add to this evidence base.

The key findings related to Research Question 2 are:

- There is a gap in the literature regarding the physiotherapy management for children with ataxia following PFT diagnosis (and the wider field of ABI)
- Challenges to rehabilitation in children with PFT are multifactorial and include child and family factors, condition related issues and physiotherapy delivery challenges.

9.3.3 Research Question 3: Is it feasible to conduct a RCT studying the effectiveness of a physiotherapy intervention (virtual training) in children with PFT?

Phase 4 provided preliminary information regarding the feasibility of conducting an RCT studying the effectiveness of VRT in children with PFT. Research question three has been partially answered. Due to low recruitment firm conclusions can not be made, however, positive findings regarding assessment have been suggested. Specific elements with regard to safety, engagement, adherence, research design, outcome measures and remote assessment are now discussed in more detail.

Safety of and Engagement with VRT

Phases 1, 2 and 3 informed the feasibility trial which demonstrated that the intervention, albeit with a small number of children, was safe to undertake and engaging for children with PFT. This is supported by a fairly extensive body of literature which has previously reported that virtual training is feasible to use in children with cerebral palsy (e.g., Ravi et al. 2017, Chen et al. 2018, and Ren & Wu 2019). Findings from this study build on emerging evidence that VRT is feasible to use in children with acquired brain injury. The findings of Phases 3 and 4 resonate with previous single case studies and series (Tatla et al. 2012, Cheung 2013), and the only previous RCT in this area described by Baque et al. (2017) who observed benefits of using a web-based gaming programme in children with ABI (30 participants in each group). Peri et al. (2019) present the largest study to date (although uncontrolled) to incorporate children with brain tumours (11 participants). No safety issues were reported, although they used an immersive clinic-based form of virtual reality training as previously noted which is different from the non-immersive training typically described in the literature and to that used in this study which included training at home. In the workshops (Phase 3) of this study, the children preferred using off-the-shelf (commercially available) video game technology as they found the games more engaging, and this informed the decision to use off-the-shelf games in Phase 4. This is in keeping with Sabel et al. (2016) who used off-the-shelf active video-gaming in their randomised cross-over trial reporting

improvements in children with brain tumours, however, since only 3 of their cohort had PFT and an assessment of ataxia was not included, it is difficult to draw comparisons. The children's preference for off-the-shelf games contrasts with the clinicians' preferences (Phase 3) who recognised the advantage of bespoke virtual training rather than off-the-shelf games as more bespoke games could adapt to children with specific physical difficulties and track progress and adherence which was then viewable to the therapist.

The feasibility randomised controlled trial was also informed by contemporary and specific evidence from Phase 2 about the use of virtual training in practice: 57% of respondents reported they were using virtual training in their practice, and, of these respondents, 73% had used it with children with PFT. However, it has been raised in the literature that despite evidence in the CP population VRT is not readily used as a first-line treatment in rehabilitation settings (Al-Nasri & Salim 2019, Levac et al. 2012, Levac & Miller 2013), with a suggestion that ongoing collaboration with health care professionals and gaming innovators should be a priority to create games that are engaging and effective. This mirrors the work completed in the Phase 3 workshops which enabled clinicians to view bespoke options for VRT and offer feedback to the companies regarding their use in practice.

Although this study has generated some answers, questions remain regarding which is the best choice of VRT moving forward for future research, particularly in view of the fast-developing technology field. Whilst off-the-shelf games, bespoke games and non-immersive and immersive technology may all be feasible to use, which, if any, are the most effective remains unanswered. Therefore, the next step for future research is to optimise this aspect of the intervention, before then seeing if VRT offers proven benefits over conventional therapy.

Adherence to training

Although findings showed positive family and child feedback regarding the VRT (from both Phase 3 and 4), adherence to the training programme both in the hospital outpatient and

home setting was lower than aimed for within the protocol. In contrast, clinical trials similar to Phase 4 by Ilg et al. (2012), and Schatton et al. (2017) which consisted of clinic-based sessions followed by home training, did not specifically report an issue with adherence to training although variability was reported; higher training intensity at home was linked with improvement in SARA scores.

Low adherence to home exercise programmes in routine clinical practice has been described before in the literature (Maring et al. 2013). Maring et al. (2013) reported that although 73% of children (n=30) with Friedreich's Ataxia were prescribed a home exercise programme, only 9% carried this out as advised. However, Sabel et al. (2016) reported good adherence to a supported home-based video gaming intervention in a similar population. In Phase 4, parents reported issues with space in conducting the VRT at home, although participation was improved when carrying out the training with siblings or family members. Levac et al. (2016) and Novak (2011) suggest ideas for improving participation in home exercise programmes, these include establishing a collaborative approach with the family and setting child-oriented goals. It has been suggested that therapy programmes that are delivered purely at home (in this case directed at upper limb function in children with cerebral palsy) can be effective (Novak et al. 2009, Novak & Honan 2019). No specific concerns regarding implementation of home exercise programmes were reported by physiotherapists in the e-survey. However, the majority of therapists were based in the inpatient setting (the primary work setting for 72% of respondents) where the focus is on inpatient rehabilitation and not home-based activities. Therefore, they may have less experience and awareness of issues in comparison to community-based therapists who would have increased insight into this area.

Attendance for hospital outpatient-based sessions for Phase 4 was also lower than the target of 12 sessions over 4 weeks (range 7-10) with a variety of reasons stated for this by parents including difficulty travelling, work commitments for parents, and educational

commitments for the child. This was despite this schedule being seen as appropriate by the PPI group and also reflecting practice by therapists identified from Phase 2. The protocol for Phase 4 of this study (12 hours of hospital-based training over 4 weeks) was slightly higher than the 8 hours clinic based for Ilg et al. (2012) who reported no issues with clinic-based attendance), and the study by Peri et al. (2019) again reported no adherence problems with a total training time of 15 hours over a one month period, indicating that this level of intensity can be achieved. Peri et al. (2019) also reported that this level of intensity resulted in an improvement in ataxia. Although there is support that higher training intensity is of benefit, the challenge remains to achieve a level of adherence which may be able to influence physical function.

Although problems with clinic-based attendance were not reported by similar studies (Ilg et al. 2012, Schatton et al. 2017 and Peri et al. 2019). The health systems in these articles (Ilg et al 2012, Schatton et al 2017 and Peri et al 2019) are not discussed, so it is unknown if receiving treatment as part of a trial which would not have been freely available (outside of the study, i.e. a non-public system) would influence adherence. It should be noted in this study (Phase 4) that the tertiary sites encompass wide geographical areas, and children may be required to travel up to 2 hours to reach their treatment hospital site. In Phase 2 of the study, clinicians did discuss the challenges for families living in different geographical areas to their child's tertiary centre. However, this was mentioned in relation to concerns over transitioning the child to local community therapy services and not the ability of the child to return to the tertiary centre for therapies following discharge home. This is because the tertiary rehabilitation service is not typically available as an option following discharge home, as therapy care (e.g., physiotherapy, occupational therapy, speech and language therapy) is usually transferred locally. Therefore, the optimum specific mix of clinic and home-based training remains under debate, balancing what is effective in theory and what would be sustainable for families in practice, whilst being deliverable for the clinicians. Understanding when the child and their family are ready to train independently at home is

important and may involve specific progression criteria to help adherence to home training. Further research is required to understand the optimum mix of clinic and home training whilst understanding the potential advantages and drawbacks of clinic-based versus home-based therapy.

Research design

A mixed methods feasibility RCT design (Phase 4) was chosen as the preferred option to examine if it was possible to conduct an RCT that would provide a high level (Level 2 OCEBM) of evidence. Similar studies of virtual training in ataxia (e.g., Ilg et al. 2012, Schatton et al. 2017) have used uncontrolled before/after no control group design but this design carries less weight to the findings due to less robust design with increased variability. The mixed methods approach used in this study allowed a more complete understanding regarding feasibility outcomes, but with potentially increased burden. In Phase 2, therapists raised lack of research evidence as a main challenge to working with children with PFT, recognising that high quality studies need to be carried out. Although a RCT is superior as a design and does offer benefits, the relatively rare nature of this condition and the low recruitment rate in this study suggest that other options (e.g., multi-site recruitment) may be of value in the future. Alternatively, Vohra et al. (2015) propose a series of n-of-1 trials for situations where large scale trials may not be feasible using a controlled design that could offer confidence in the results.

In this study, despite lower than anticipated recruitment, the actual process of randomisation was not a particular barrier to recruitment. All participants who were recruited were willing to be randomised, although one participant's parent did express their disappointment in their exit interview at not receiving the intervention. Difficulties in recruitment for the feasibility trial have been extensively reported in Chapter 8, and it is of note that recruitment to the workshops (Phase 3) of this study was also a challenge. Participants who expressed their interest but who were unable to attend the workshops, cited similar reasons to those

noted within the trial and these included time and work commitments and not wanting their child to miss school. Comparing the recruitment rates in Phases 3 and 4 (6-40% site dependent) with the recruitment rate to Phase 1 (92%) where children and their families did not have to attend on site for any additional visits confirms these issues as barriers to recruitment. This suggests that future trials should be as flexible as possible in their research design to allow any on-site visits to be family-friendly, such as offering after school appointments and considering timing assessments to coincide with school holidays (e.g., 8 weeks apart) to minimise time out of school.

Assessment/outcome measures

The assessment schedule and choice of outcome measures in Phase 4 was feasible to carry out. Only 2 out of 30 assessments were missed/not undertaken during the feasibility RCT, and no concerns were raised about the length of assessments, with families reporting that this was similar to their usual clinical appointments. Assessment length is rarely detailed in the literature although evidence from Phase 2 reported a broad consensus that typical physiotherapy sessions are between 30-60 minutes. All outcome measures were completed in 15 out of 24 (63%) face-to-face appointments, and they encompassed ataxia scales, assessment of upper limb coordination, a balance scale, functional mobility, and a quality of life measure specific to brain tumours. The SARA and BARS were completed in 96% and the Paediatric Balance Scale 100% of face-to-face assessments. This is in keeping with other similar studies e.g. such as Peri et al. (2019) who reported no issues with undertaking a range of assessment incorporating ataxia, balance and functional outcomes.

Choice of outcome measures for the feasibility RCT was informed by Phases 1 and 2. Phase 1 confirmed that ataxia scales were appropriate to use as outcome measures, with the advantages of the SARA discussed earlier, along with support in clinical practice for the SARA from Phase 2 of this study. However, the wide variety of outcome measures used

both clinically (as demonstrated in the e-survey in Phase 2) and in research as evident from the literature search (Hartley et al. 2019) creates difficulties for comparison across studies. The apparent trend in clinical research in this area is to use the SARA along with participation measures where the focus is on ataxia/balance outcomes (Ilg et al. 2012, Schatton et al. 2017, Peri et al. 2019). Although not the main focus of this study, it is clear that there is a lack of standardised activity and participation measures for children with brain tumours.

The ceiling effect of the PEDI was noted in Phase 1, prior to this study this has not been reported formally as a problem but was clearly an issue with 18% of children reaching the top threshold, indicating best possible function, at baseline assessment (and a higher effect at subsequent time points). Therefore, options for assessment of function and activity remain an area of research interest. The PEDI was initially chosen as it was the only validated outcome measure of functional ability in children with acquired brain injury (Haley et al. 1992), and the MCID has been reported (Iyer et al. 2003). In the initial CARS work there was an association of the mobility domain of the PEDI with ataxia severity (Hartley et al. 2015). However, longitudinal correlation was not observed in Phase 1, potentially influenced by the ceiling effect. The PEDI does have the advantage of being able to be completed by the therapist or by parental questionnaire, and individual subdomains (physical, self-care and social interaction) can be completed as stand-alone sections. Utilising the care giver section of the PEDI may provide a potential option that could demonstrate increasing independence which may be meaningful to the child and family. Alternatively, an electronic version of the PEDI (PEDI-CAT) (Haley et al. 2005), is also in use which may address the ceiling effect of the original PEDI, and this has now been assessed in inpatient post-acute rehabilitation (Fragala-Pinkham et al. 2016). However, the PEDI-CAT remains focused on activity and does not strongly reflect participation. Further examination of participation measures and child/patient reported outcome measures would be beneficial to ensure there is the ability to accurately measure change in areas that are

meaningful to the child and family. Identifying key activity and participation and fatigue measures that could be used alongside the SARA would be of value to achieve consensus in a core set of outcome measures to be used across clinical practice and in clinical trials.

Remote video assessment/intervention

Due to the implications of COVID-19, amendments were made to the Phase 4 protocol, initially to enable remote video assessments, and then subsequently to facilitate the option of remote video intervention sessions (Chapter 8). This reflected the way in which remote service video intervention rapidly became introduced across NHS practice in 2020 in response to the pandemic. The Chartered Society of Physiotherapy offered guidance for its implementation (CSP 2020a) and a national evaluation of remote service is currently underway (CSP 2020b). Although this change was driven by COVID-19 it does provide advantages for children and parents who would normally have to travel a long distance to attend their tertiary centre for assessment.

Two participants were recruited to the usual care group after the first wave of the pandemic when remote video assessments were available, but both these families preferred face-to-face assessments. Both families had previous experience of remote video assessments by the tertiary centre during 'lockdown' due to unavailability of local community services because the physiotherapists had been redeployed. This experience aligns with a report by the Teenage Cancer Trust (2020) that notes physiotherapy was the most affected discipline with 69% of teenagers and young people with cancer surveyed reporting they saw their physiotherapist less often than usual during the first wave of the pandemic. The Phase 4 families reported they felt a face-to-face appointment was preferable as there was a perceived sense of reassurance of seeing a therapist in person having experienced a lack of opportunity to do this during the pandemic. There was also a general sense of reassurance from being in the study (from the usual care group pre and post COVID-19) which was thought to offer enhanced monitoring which is in keeping with other cancer trials

(Nurgat et al. 2005), but not necessarily reported in rehabilitation trials previously. Lack of community therapy service provision and difficulties transitioning children to community services had been identified as an issue by physiotherapists in the e-survey (completed prior to COVID-19), suggesting that the additional impact of the pandemic on already stretched local services could lead to a significant gap in services for children requiring on-going rehabilitation following brain tumour diagnosis. It is already known that survivors of childhood cancer demonstrate reduced levels of activity and lower physical health outcomes (Oeffinger et al. 2006), with particular balance issues in children with PFT (Piscione et al. 2014). Therefore, it would seem important to support children and their families to continue to engage in activity and, where appropriate, individualised therapy programmes. The impact of reduced availability of local therapy services during the COVID-19 pandemic is not yet clear and neither is it clear whether rehabilitation care for ataxia after the COVID-19 pandemic will continue to use increased remote delivery; this is an area of future research.

Remote video intervention sessions were not undertaken as part of this study as participants recruited post COVID-19 were allocated to the usual care group. The intervention does appear possible to supervise remotely (similar to the study by Sabel et al. 2016), whereas more traditional 'hands on' neuro rehabilitation approaches do not lend themselves to remote provision. Feasibility and effectiveness of remote intervention sessions therefore require further exploration.

One assessment was conducted remotely and specific details regarding remote assessment of each outcome measure were presented in Chapter 8. In particular the eye movement item of the BARS examination is challenging to assess by remote video assessment. The developers of the BARS reported a lower internal consistency with the eye movement item (during face-to-face assessment) but justified the inclusion of this item stating that scores of limb coordination and gait or speech cannot accurately predict eye movement score, and that identification of eye movement difficulties is an important part of

the clinical picture due to its common involvement in genetic ataxias (Schmahmann et al. 2009). Children with PFT can commonly present with visual difficulties (in Phase 4, 3 out of 10 participants were observed to have eye movement difficulties according to the INAS assessment). However, in PFT there are additional problems such as cranial nerve lesions and this is evidenced in the literature. E.g., Wilne et al.'s (2007) meta-analysis reports that at diagnosis 42% of children with brain tumours present with cranial nerve problems including abnormal visual fields, or $6^{th}/7^{th}$ nerve palsy. Therefore, although visual assessment is of value in this population, the eye movement item for the BARS is unreliable as it can be also influenced by cranial nerve deficits or increased intracranial pressure and formal ophthalmology assessment is therefore required in children with PFT. The findings from Phase 4 show that the SARA can be fully completed via both face-to-face with potential for remote assessment (with assistance of family members to position the camera and for finger to nose testing) and this finding enhances the confidence that researchers can have in the utility of the SARA for future studies.

Additionally, there are now developments using technology to assist with remote assessment to increase accuracy. This includes sensors and wearable technology and recent advances have led to the development of the SARA-home (Grobe-Einsler et al. 2021), as presented in Chapter 8.

Although there were concerns raised with the ceiling effect of the PEDI it does lend itself to remote assessment due to its ability to be completed by parental questionnaire. This was also true for the PedsQL Brain tumor module. Remote video consultations have been noted to be valuable clinically in a similar field of paediatric haemophilia (Flannery et al. 2020). However, physiotherapists did express concerns regarding its use in the future suggesting that although it is not a direct replacement for face to face assessment, remote assessment does offer opportunities to triage and offer advice particularly if patient travel is difficult.

Providing an overall assessment of feasibility and determining progression to a full RCT is difficult. It is recognised in the literature that although there are established methods to report feasibility trials (Eldridge et al. 2016), there are no clear criteria for determining if feasibility trials should be progressed (Mbuagbaw et al. 2019). However, recent studies have demonstrated methods of establishing multidisciplinary collaborative stop/go criteria (pre commencement of study) (Young et al. 2019), alongside emerging frameworks for understanding acceptability of interventions (Sekhon et al. 2017) which might be of value to consider when further Phase 4 data are available to assist with final feasibility recommendations. There have also been suggestions on decision making processes following feasibility trials to optimise strategies and solutions to allow progression to full trials e.g. ADePT (A process for Decision-making after Pilot and feasibility Trials (Bugge et al. 2013) which may also be of benefit to consider.

In summary, this study has provided initial information regarding the feasibility of conducting an RCT examining VRT in children with PFT. The research question has been partially answered, although a number of protocol considerations (e.g. intensity of intervention, mix of home/clinic sessions and inclusion criteria) need to be explored further before considering a larger scale trial. It is also likely that additional recruitment strategies would be required to allow study progression. Phase 4, as a self-contained study is continuing until December 2021, to enable further data collection to consolidate findings and any final feasibility recommendations will be made at the end of the study extension.

The key findings related to Research Question 3 are:

- VRT is engaging to use in children with PFT and no safety issues have been identified to date;
- Reduced adherence to VRT occurs both in the hospital and home setting;
- Challenges to recruitment exist and recruitment is influenced by factors such as time commitment and travel;

- Selected outcome measures appear feasible to use although future studies would benefit from a validated participation measure; and
- Potential exists for remote assessments.

9.4 Limitations/Strengths

In this section the strengths and then the limitations of the study are critically considered.

9.4.1 Strengths of the study

The key strengths of the study are engagement with children and their parents, involvement of clinicians, coherence between phases of the study and adaptability to cope with changes required due to the global pandemic. These are now presented in more detail.

Involvement and engagement with children and their parents: a strength of the study was the significant involvement of children and their parents during Phases 1, 3 and 4 of the study; this involvement was both through PPI and creating a design that created opportunities for children and parents, as research participants, to share their perspectives and ideas about their experiences.

Prior to the commencement of the phases, a PPI group was formed to explore research questions that children and parents thought were important to address and these guided the initial development of the phases. During the project further engagement was undertaken both through a parent advisor on the Steering Group and via feedback from families who entered the initial CARS study (who formed a PPI group). Feedback was provided to enable refinement of research questions and also on the process of assessment and use of outcome measures e.g., whether the length of assessments was acceptable. Involvement of children and their families who participated in the workshops also occurred in Phase 3 and the children's thoughts regarding choice of games at the workshops was key to informing Phase 4. Using a mixed methods approach for Phase 4 enabled the

opinions of the children and their parents who were research participants to be explored (e.g. through exit interviews). This provided valuable insights into understanding adherence to attending for assessments and undertaking the intervention where applicable.

Involvement and engagement of clinicians: Clinicians' involvement occurred through each phase of the study. The emphasis was on physiotherapists' views in the e-survey (Phase 2) through their involvement as research participants, however, they were involved in all phases of the study. Feedback from physiotherapists acting as raters was collected during the initial CARS study to understand clinicians' views of the use of the SARA and BARS in children with PFT. Clinicians also attended the workshops as participants (Phase 3 of the study) and were able to observe children using the gaming options whilst also trying them out themselves to allow physiotherapist feedback regarding the clinical utility of the games. Their involvement added strength to the study as it meant that the decisions made were grounded in the reality of practice and provided immediate feedback by experts in their field. During Phase 4 of the study, there was ongoing feedback by the assessor and intervention therapists highlighting any issues or challenges to either assessment or use of the VRT.

The study has encompassed the views of children, parents and clinicians; a strength of this is that this should enable the findings to be more easily integrated into clinical practice.

Coherence between phases of the study: A strength of this study is that there is a coherent link between each of the phases. The initial research priority was to establish accurate assessment by examining the psychometric properties of ataxia scales in children with PFT for the first time. Validated outcome measures which have been evaluated in the chosen population group are fundamental to the success of any future clinical trial that is attempting to determine if change has occurred.

The next step was to understand current clinical practice as there was a particular lack of research in this area as highlighted in the literature review. Understanding current clinical practice also established expert opinion and provided a basis for refining the protocol for the feasibility trial. This led to further exploration of children and parents' views in the workshops to ultimately inform the final feasibility RCT. The feasibility RCT allowed progress towards the parents' research priorities raised in the PPI group as they wanted to know how much and what type of physiotherapy is best to carry out.

All phases interlinked and provided information which scaffolded the knowledge found in individual phases as explored earlier in the discussion.

Clinical relevance: All phases of the study are also clinically relevant with elements that can be incorporated readily into practice, this is discussed further in the recommendations for clinical practice. Clinicians can be confident that the SARA is practical to use in children with PFT and can measure change in the severity of ataxia in this population. The study indicates that VRT is feasible to incorporate into practice, but its effectiveness needs to be determined in larger RCTs, considering the mix of home based and clinic interventions which again reflects challenges of clinical practice. The addition of video remote assessments to the feasibility RCT (Phase 4) reflects the reality of change in practice during the COVID-19 pandemic and provides further insights regarding this.

Adaptation to the impact of COVID-19: Although there were challenges due to the impact of COVID-19, particularly regarding suspension to recruitment, actions were put in place quickly and the study was adapted to include new processes, as required. Initially risk assessments were carried out to cover multiple elements of the overall study, e.g. Phase 1 and Phase 4 recruitment and follow up, financial implications, and time lost to the fellowship due to additional clinical commitments. The design of Phase 4 of the study was adapted and gained ethics approval for the option of remote video assessments and intervention. Phase 4 already included a home-based element which proved very relevant within the

pandemic and enabled flexibility with the addition of remote appointments as required. The host site was able to re-open in a timely manner with evidence of risk assessments in place to support the continuation of the study.

9.4.2 Limitations of the study

The main limitations of the study are delays in opening sites (Phase 3 and 4), low recruitment rate (Phase 3 and 4), small sample sizes (Phase 1, 3 and 4), underpowered findings (Phase 1), inability to keep pace with changes in technology (Phase 3 and 4), lack of gold standard outcome measure (Phase 1 and 4), lack of long term follow up (Phase 4) and limited detail in stop/go criteria to assist with decision making regarding assessment of feasibility (Phase 4). Some of these limitations reflect issues that the researcher could not control, and others reflect the state of play within the field. These limitations are now presented in more detail.

Delays in opening sites (Phases 3 and 4): Phase 3 was held with participants recruited from a single site (main sponsor site) instead of the planned two sites due to delays in the second site's local Research and Development approval and local capacity processes. Gaining a wider spectrum of views may have been advantageous to further inform the protocol for Phase 4 of the study.

There were further delays in opening sites for Phase 4 of the study, due to local approval processes, and additional steps required to reopen post COVID-19 again which accrued delays which in turn acted as a barrier to recruitment.

Recruitment Rate (Phases 3,4): Recruitment rate was low for Phase 3 (31%) and Phase 4 (6-40% site dependent) of the study, in comparison to Phase 1 which was high (92%). Recruitment rate to Phases 3 and 4 was influenced by the time and commitment required (for parents and their child) to these phases of the study, whereas Phase 1 did not require any additional hospital visits, and assessments were in line with those conducted as part of

routine clinical care. Although Phase 4 was ultimately conducted over four sites, recruitment remained low as discussed in Chapter 8. Recruitment was particularly problematic in sites other than the host site) as these sites had no dedicated trial coordinator time. However, Phase 4 was a feasibility study, and the aim was to examine issues such as recruitment and adherence to intervention and not determine effectiveness of the intervention itself, and thus the specific objectives of Phase 4 were still able to be achieved.

Sample size (Phases 1, 3 and 4): One of the main limitations of this study is the small sample sizes in the three phases of the study. This is inherently linked to the fact that although brain tumours are the most common solid tumour occurring in children, overall, it remains a rare disease. There are approximately 500 new cases of brain and spinal tumour in children and adolescents diagnosed in the UK per year (NHS Specialised Services 2010), and thus each tertiary centre manages a small population group. This also led on occasion to the same children and families being involved in more than one phase of the study, and although families often demonstrated a keen commitment to engage in this process, the demand on families should be considered (particularly as they typically would have been involved in other research studies as part of their neurosurgical/oncology treatment).

Specifically, for Phase 1, this study was conducted on a single site, therefore limiting the potential sample size. When considering Phase 4, it was also highlighted that fewer children than expected in the first two sites (from the pre-existing databases audited in the design stages) were presenting with ataxia sufficiently significant to be included in the study within the specified age range. This again limited the potential sample size. As discussed in Chapter 8 this may be related to a reduction in incidence of cerebellar mutism syndrome which is often associated with more severe ataxia. New sites were opened to help mitigate this problem although ongoing recruitment issues (discussed previously) at other sites was also noted.

Underpowered findings (Phase 1): Although recruitment rate was high for Phase 1 of the study, when subgroup analysis was considered, there were only small numbers in different analysis groups e.g. tumour type. Therefore, Phase 1 was underpowered to detect significant changes. Results were therefore reported as potential trends (instead of completing statistical testing for significance). If other sites had been involved in Phase 1, the addition of their data would likely have created sufficient numbers for subgroup analysis to be undertaken and would have provided greater confidence in the results. This is discussed further in recommendations for future research.

Inability to keep pace with technology (Phases 3 and 4): Advances in technology which outpaced the conduct of the study is also a limitation of this study, although this is inevitable considering the speed in the changes to gaming technology. Planning and implementing the trial requires a considerable period of time during which the technology for virtual training is constantly progressing, therefore it is hard for the design and choice of intervention to keep pace with developing technology and to be relevant in terms of recommendations. Indeed, as previously discussed, although the Kinect is no longer being manufactured, it is still being integrated into bespoke rehabilitation virtual training packages. The need to consider evolving technology when planning virtual training programmes is clear. Keeping informed of new technologies and using devices with the most flexibility of use and compatibility with other devices may help in planning future trials. These challenges also shift the importance to investigating the general concepts that underlie the technology e.g. the concept of a variable cognitively demanding game versus a repetitive chore as these concepts can be replicated even if the specific technology changes.

Lack of gold standard outcome measures (Phases 1 and 4): A further issue that impacted on the study was a lack of gold standard outcome measure to test the ataxia scales against or to use as a definitive outcome measure in the trial. This led to the need to further validate the SARA and BARS in this population group. However, the lack of an

existing gold standard outcome measure often presents a challenge in rehabilitation research. It is unusual to find an outcome measure that has been validated to consider all psychometric properties in specific populations. All properties of outcome measures including validity, reliability and responsiveness should be examined to allow full confidence in the outcome measure to be used in clinical trials (Scholtes et al. 2011). The use of the SARA (and BARS to a lesser extent) has been supported by the results of this study, however, as highlighted before, it may be best practice to combine these alongside participation based and patient-reported outcome measures as a set of core outcome measures as discussed earlier.

Lack of long term follow up (Phase 4): A criticism of studies reviewed in the literature search of related interventional trials was a notable lack of long-term follow-up for participants. Only two studies of the 11 reviewed in detail reported outcomes beyond one-month post-intervention ('intermediate period'). All other studies reported short term results only (0-1 months post intervention). In Phase 4 of this study, the follow up assessment was 6 weeks post-completion of intervention and it is acknowledged that any further research should consider a later timepoint for follow-up assessment. The follow-up timescale for the feasibility RCT for this study was influenced by practical reasons of length and costing of the study. However, a longer follow-up would be of value to determine if any potential benefit is retained, or if this reduces over time which may indicate the need for further blocks of intervention.

Limited detail in stop/go criteria to assist with assessment of feasibility (Phase 4): The pre-determined stop/go criteria for the study included a set target for recruitment and there was no set threshold for other recognised factors such as drop out and completion of outcome measures. Literature regarding assessment of feasibility has been presented in Chapters 8 and 9, and a collaborative more detailed approach to setting stop/go criteria prior to the RCT commencement may have been beneficial. Emerging frameworks on

decision making post feasibility trial can be used when the complete data set for Phase 4 is available.

9.5 Recommendations for future research

This study has provided information on appropriate ataxia scales to assess ataxia severity in this population group, evidence of current international physiotherapy practice and the feasibility of conducting a RCT examining virtual training in children with PFT, thus beginning to address gaps in the literature. However, further areas of research have been identified during this programme of work which are presented below.

Outcome measures

1) Further validation of psychometric properties of ataxia scales

A study is needed to confirm the minimally clinically important difference of the SARA and BARS relative to children's age. This could be undertaken by achieving consensus of clinician opinion, or a multisite study examining change in ataxia score related to change in symptoms (similar to Phase 1, but fully powered). This study would provide further evidence for the use of these tools in clinical trials and offer clinicians a benchmark for evaluating the efficacy of interventions.

Additionally, examination of the subset of the Bal SARA should be undertaken to determine reliability, validity, and responsiveness in children with ataxia. This could include children younger than 4 years of age to see if it can be used with pre-school children (e.g. age 2-4 years) as there is currently no standardised measure of ataxia in children under the age of 4 years.

Further exploration of the feasibility of remote assessment would also be of value in view of changing practices as a result of COVID-19. This could include validation of the SARA-Home in the paediatric population.

2) Core set of outcome measures for children with PFT

A study using Delphi survey consensus method, involving clinicians and families, could be undertaken to establish a core set of outcome measures for children with PFT. The SARA could be used as a measure of ataxia, however, it should be combined with additional measures of activity, participation, fatigue and patient/child reported measures. Further exploration of participation measures and child/patient reported outcome measures would also be beneficial to ensure accurate measurement of change in areas that are meaningful to the child and family. This is important as there is a particular gap in participation/child reported measures for children with PFT and the wider field of ABI, and the ceiling effects of the PEDI were noted in this study. Experience could be drawn from measures in use for children with cerebral palsy as more established tools already exist e.g., Children Participation Questionnaire (CPQ) (Rosenberg et al. 2010).

Ataxia in children with PFT

1) Risk factors for ataxia

The risk factors for more severe ataxia (i.e. medulloblastoma and midline tumours) should be explored with a larger dataset to confirm (or otherwise) the findings of this study. This will be achieved to a certain extent via the NORPHO CMS study (NCT02300766) which aims to provide an international multisite dataset (to date, nearly 500 participants have been recruited across ten countries). Although the specific focus of the NORPHO study is on cerebellar mutism, it does include assessment of ataxia using the BARS and SARA pre-operatively, post-operatively, 2 months post operatively and 1 year post operatively; this will allow further examination of the course of ataxia. Multivariate analysis considering tumour histology (including molecular sub-type), surgical approach, tumour location with more detailed MRI imaging analysis (e.g. tumour volume, signal characteristics), and genetic factors will enable a clear picture of risk factors associated with more severe ataxia. More

detailed imaging analysis would further inform the pathophysiological basis for persistent ataxia in this population. Cut off values for the SARA and BARS developed from the CARS study are being used in the NORPHO study, and I and members of the supervisory team are involved in discussions regarding data analysis of the NORPHO study.

2) Associated clinical features

A prospective observational multisite study should be considered to enable analysis of associated clinical features (e.g. oculomotor issues and audiovestibular dysfunction) that occur with ataxia and to determine any correlation with severity of ataxia. Although children with PFT can commonly present with these issues there is a lack of literature in this field. In the first instance the CARS study can be used to refine potential data analysis which can then be repeated with a larger dataset taking into account the clustering effect within a treatment centre.

Rehabilitation

1) Challenges to rehabilitation

A longitudinal qualitative study would be of merit in exploring parent and children's views of challenges and experiences of rehabilitation at key stages of their rehabilitation journey (e.g. in the acute phase whilst in hospital, whilst at home but still undertaking oncology treatment, and following completion of any adjuvant treatment). A particular focus on engagement and expectations of rehabilitation would help to inform both clinical practice and clinical trials in this area.

2) Effectiveness of rehabilitation

A large well controlled trial should be undertaken to determine the effectiveness of physiotherapy intervention for children with PFT. If/when the effectiveness of VRT is established then it may be appropriate to then move forward to a 'superiority trial' e.g. to

see if VRT offers benefits over conventional therapy. However, before this is designed, further research will be required to answer key questions raised in this study regarding not only the optimum timing of the intervention, but also regarding the intervention in terms of dosage, keeping pace with technology and the mix of hospital and home-based training.

Establishing virtual training in clinical practice should also consider the potential resource-related barriers raised by clinicians in the e-survey (e.g. access and funding for equipment and training for staff, and condition-specific clinical issues), which particularly related to the acute post-operative setting.

In summary, lessons learned from this study can help to frame future research questions and thus trials.

A novel way of summarising the key elements for future research is through using the domains of the 'PICO' framework (Patient/population, Intervention, Control/Comparison Group, Observations/Outcome) (Table 9.1); all of these domains have been explored during this study.

Table 9.1 PICO framework: Effectiveness of rehabilitation for children with ataxia following surgical resection of PFT

Domain	Key factors for consideration in future research
Patient/population	• Focus should be on children (aged 4-18) following surgery for PFT (due to established ability to use outcome measures and engage in length of assessment in this age range). • Optimal timing post-surgery remains under debate; this study (and literature) suggests 3 months to 4 years depending on adjuvant treatment. • Consider inclusion of children with ataxia from other ABI pathologies involving the cerebellum (e.g. vascular/traumatic insults) as this would increase potential participants for future research. • Consider stratifying participants into those likely to have persistent problems with potential to benefit from intervention, e.g. using extent of radiological injury. • Characterise comorbid impairments (e.g. audiovestibular/visual impairment) and social-environmental factors that may predict those who can complete treatment or need particular intervention.
Intervention	• VRT offering motivational treatment option that includes variation in repetitive practice associated with reinforcement learning principles • Progression criteria to determine when child is ready to train independently at home • Balance of hospital and home-based training. • Consider role of the physiotherapist in the intervention (e.g. progression of training). • Off-the-shelf compared with bespoke gaming. • Option of remote video appointments. • Dosage continues to require careful consideration; this study (and literature) suggests of 15 hours of training in total but the length of intervention period remains unclear. • Need to continue to assess fidelity of delivery of intervention.
Control/Comparison	• Usual care (with recording of what this consists of). • Or alternative low-tech control intervention with equal amount of time spent on task or attention from therapist.
Observations/Outcome	• Use SARA as part of outcome measure set. • Incorporate impairment, activity, and participation measures. • Series of assessments to include long term follow up. • Option of remote assessments. • MRI findings as comparison i.e., effect on imaging of training similar to other studies.

9. 6 Outcomes, ongoing work and dissemination

The outcomes of this study have resulted in new work being developed, contributions to clinical pathways, feedback to parents and dissemination via conferences and published papers. The aim with much of this dissemination has been to reach special interest groups (e.g., those with specific interests in children's neuro-oncology, neuro-surgery, acquired brain injury, physiotherapy, speech and language therapy). These achievements are now presented.

Identification of gaps in evidence-base

This study has identified clear gaps in the evidence base for physiotherapy management for children with ataxia from any pathology, with particular reference to children with PFT. The literature search has been published to disseminate the work to clinicians and academics and to provide evidence of the need for further research in this area (Hartley et al. 2019).

The CARS study has also been extended further (not reported as part of this Thesis) to now examine any interaction between cerebellar ataxia and associated difficulties found in children with PFT: oculomotor and audiovestibular dysfunction. This aims to identify any association with severity of ataxia and these issues in association with analysis of MRI findings. This will further address a gap in literature as these impairments, their association with ataxia and potential impact on the design of interventions have not been explored before.

Assessment outcome measures

This study has built on the original CARS study and provided new evidence regarding the use of the SARA and BARS in children with PFT. This has been disseminated via conferences to carefully targeted special interest groups. Preliminary data were initially presented to clinical audiences via a poster presentation at ISPNO 2018 (International

Symposium of Paediatric Neuro-Oncology) and presentation at the Posterior Fossa Society Meeting in Iceland in 2018. Further data were planned to be presented at the ESPN 2020 Conference (European Society of Paediatric Neurosurgery); however, this was delayed due to COVID-19. The longitudinal nature of ataxia and risk factors are to be reported in a paper (CARS paper submitted December 2020 to Child's Nervous System); this will reach both clinicians and academics.

Parents of children involved in the CARS study have received individual feedback regarding their assessment results if they wished to view these. A summary of the CARS study is planned to be available on the North West Neurosciences Network website for families to view.

The North West Neurosciences Network Therapy group is also currently devising a neuro-oncology patient pathway. This aims to map the child's journey to coordinate the admission and pre-operative process, ensure timely access to all relevant specialities during their admission, promote effective communication and coordinated discharge planning. Information gained from this study regarding length of time for assessments and potential significant long-term rehabilitation needs for some children has informed preliminary discussions for the pathway.

Identifying current physiotherapy practice

The e-survey provided original information about current physiotherapy practice for children with ataxia following PFT surgery. This was disseminated to professionals in this area via a presentation at the BPNA 2020 (British Paediatric Neurology Association) Neuro-Oncology Study Day. Subsequent to this it has been published for wider dissemination via a paper in Journal of Rehabilitation Medicine Clinical Communications (Hartley et al. 2020). The survey tool has also since been used as a base for the REACH study by the Posterior Fossa

Society to examine therapy practice for other disciplines (e.g. Occupational Therapy and Speech and Language Therapy). This will be disseminated at the next PFS meeting in 2021.

Information from this programme of research on consensus of expert practice internationally and use of outcome measures is also informing the work by the Paediatric Oncology and Paediatric ABI Physiotherapy Networks with the aim of producing clinical guidance for therapists in this area. The objective of this is to produce a gold standard clinical therapy pathway which would include recommended criteria (and timing) of referrals, use of validated standardised outcome measures, recommendations for therapy input in the acute and community setting and discharge planning.

Feasibility RCT

Individual participant assessment results are fed back to the child and their parents (and community physiotherapists at the parents' request) following completion of their participation in the feasibility RCT. A summary of the trial will be made available to all families on completion of the feasibility RCT. The trial protocol was disseminated to the clinical audience via a poster presentation at the BPNA Study Day in 2020. As mentioned previously, Phase 4 study remains open (until December 2021) to enable ongoing recruitment to confirm feasibility findings.

9.6 Recommendations for future practice

This study has demonstrated findings that can be immediately integrated into clinical practice.

Outcome measures

1) Pre- and post-operative assessment

Standardised outcome measures should be used pre- and post-operatively to assess ataxia in children with PFT aged 4 to 18 years. This should include an assessment of ataxia but also consideration of activity and participation measures following surgery. A combination of outcome measures is feasible to undertake and complete in children who are more than 1 year following surgery.

2) Use of SARA (+/-Bal SARA) as part of core outcome set

The SARA scale should be incorporated into clinical practice to assess severity of ataxia. Regular reassessment using the SARA scale is also feasible and the use of this at specified time points allows comparison of progress across different patient groups. The use of the Bal-SARA subset could be considered if all items cannot be assessed; however, the use of this in children with PFT requires further investigation. There is scope to consider a multicentre prospective registry of outcome measures (e.g. similar to the original North Star model in the neuromuscular field (Muscular Dystrophy UK 2020)) to enable consistent recording of outcomes across multiple sites.

3) Caution with use of PEDI

In children with milder ataxia caution should be taken if relying on evaluation using the PEDI mobility domain as a ceiling effect is evident. Alternative options utilising the care giver assistance scale or the PEDI-CAT have been discussed.

Risk factor identification

1) Potential for more severe ataxia in children with medulloblastoma and midline tumours

The knowledge of risk factors for more severe ataxia should be used for early identification of children with potential need for long-term rehabilitation.

Use of VRT

1) Option for VRT in clinical practice

VRT has the potential to be used in clinical practice as demonstrated by this study and supporting literature, and Phase 2 demonstrated that it is already being used by clinicians. However, its effectiveness has yet to be determined, therefore although possible to integrate into children's treatment as an engaging and motivating option, further consideration is required. Phase 3 also demonstrated that bespoke VRT options are also becoming available on the market and an awareness of these could also be considered when planning a child's therapy programme

9.7 Conclusion

This PhD programme of work has provided new insights into an identified gap in the literature considering physiotherapy assessment and management of children with ataxia following surgical resection of PFT. It has answered the specified research questions regarding identification of outcome measures, understanding the current scope of physiotherapy interventions and challenges to rehabilitation and determining the feasibility of conducting an RCT examining VRT, whilst considering the children's and parents' views of VRT.

Key findings include the responsiveness of the SARA, preliminary suggestion for a MCID, risk factors for severe ataxia and the identification of multifactorial challenges to rehabilitation.

This study has provided initial information regarding the feasibility of conducting a RCT examining VRT in this population group, whilst refining areas for further research. Significant information to inform future trials has been learnt throughout the study including:

- how to define the patient group (inclusion and exclusion criteria including time since surgery) under study;
- baseline observations (including neuroradiology and histology) that can stratify patients into those likely to have persistent problems and/or those most likely to benefit from intervention;
- assessment scales and tools to measure the level of impairment and disability and confounding factors;
- outcome tools and their properties such as responsiveness to change;
- methods of analysing these outcomes;
- designing the intervention based on previous work in related areas;
- designing an overall trial protocol;
- re-defining the participants, assessment tools, intervention and protocol in the light of practical experience in the feasibility study

In summary, this study has contributed new knowledge to this field and revealed that further research is needed on guidelines for treatment, core sets of measures, and effective therapy modalities with consideration of optimum timing and dosage of intervention.

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Appendices

Appendix 1 – Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hubsch et al. 2006)

Rater:_____date: _____patient_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait	2) Stance
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.
0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed) 1 Slight difficulties, only visible when walking 10 consecutive steps in tandem 2 Clearly abnormal, tandem walking >10 steps not possible 3 Considerable staggering, difficulties in half-turn, but without support 4 Marked staggering, intermittent support of the wall required 5 Severe staggering, permanent support of one stick or light support by one arm required 6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person) 7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person) 8 Unable to walk, even supported	0 Normal, able to stand in tandem for > 10 s 1 Able to stand with feet together without sway, but not in tandem for > 10s 2 Able to stand with feet together for > 10 s, but only with sway 3 Able to stand for > 10 s without support in natural position, but not with feet together 4 Able to stand for >10 s in natural position only with intermittent support 5 Able to stand >10 s in natural position only with constant support of one arm 6 Unable to stand for >10 s even with constant support of one arm
Score	Score

3) Sitting	4) Speech disturbance
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.	Speech is assessed during normal conversation.
0 Normal, no difficulties sitting >10 sec 1 Slight difficulties, intermittent sway 2 Constant sway, but able to sit > 10 s without support 3 Able to sit for > 10 s only with intermittent support 4 Unable to sit for > 10 s without continuous support	0 Normal 1 Suggestion of speech disturbance 2 Impaired speech, but easy to understand 3 Occasional words difficult to understand 4 Many words difficult to understand 5 Only single words understandable 6 Speech unintelligible / anarthria
Score	Score

1

Rater:_____date: _____patient:_____

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband's reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0** No dysmetria
- **1** Dysmetria, under/ overshooting target <5 cm
- **2** Dysmetria, under/ overshooting target < 15 cm
- **3** Dysmetria, under/ overshooting target > 15 cm
- **4** Unable to perform 5 pointing movements

Score	Right	Left
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0** No tremor
- **1** Tremor with an amplitude < 2 cm
- **2** Tremor with an amplitude < 5 cm
- **3** Tremor with an amplitude > 5 cm
- **4** Unable to perform 5 pointing movements

Score	Right	Left
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0** Normal, no irregularities (performs <10s)
- **1** Slightly irregular (performs <10s)
- **2** Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
- **3** Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
- **4** Unable to complete 10 cycles

Score	Right	Left
mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0** Normal
- **1** Slightly abnormal, contact to shin maintained
- **2** Clearly abnormal, goes off shin up to 3 times during 3 cycles
- **3** Severely abnormal, goes off shin 4 or more times during 3 cycles
- **4** Unable to perform the task

Score	Right	Left
mean of both sides (R+L) / 2		

Appendix 2 – Brief Ataxia Rating Scale (BARS) (Schmahmann et al. 2009)

Gait
0: Normal
1: Almost normal naturally, but unable to walk with feet in tandem position
2: Walking without support, but clearly abnormal and irregular
3: Walking without support but with considerable staggering; difficulties in half turn
4: Walking without support not possible; uses support of the wall for 10-meter test.
5: Walking possible only with one cane
6: Walking possible only with two canes or with a stroller
7: Walking possible only with one accompanying person
8: Walking impossible with one accompanying person (2-person assist; wheelchair)

Knee-tibia test (decomposition of movement and intention tremor) (Left and Right scored)
0: Normal
1: Lowering of heel in continuous axis, but movement is decomposed in several phases, without real jerks, or abnormally slow
2: Lowering jerkily in the axis
3: Lowering jerkily with lateral movements
4: Lowering jerkily with extremely long lateral movements, or test impossible

Finger-to-nose test (decomposition and dysmetria of arm and hand) (Left and Right scored)
0: Normal
1: Oscillating movement of arm and/or hand without decomposition of the movement
2: Segmented movement in 2 phases and / or moderate dysmetria in reaching nose
3: Segmented movement in more than 2 phases and / or considerable dysmetria in reaching nose
4: Dysmetria preventing the patient from reaching nose

Dysarthria
0: Normal
1: Mild impairment of rate/rhythm/clarity
2: Moderate impairment of rate/rhythm/clarity
3: Severely slow and dysarthric speech
4: Speech absent or unintelligible

Oculomotor abnormalities
0: Normal
1: Slightly slowed pursuit, saccadic intrusions, hypo/hypermetric saccade, nystagmus
2: Prominently slowed pursuit, saccadic intrusions, hypo/ hypermetric saccade, nystagmus

TOTAL (out of 30)

Appendix 3 – Systematic review paper

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REVIEW

Exercise and Physical Therapy Interventions for Children with Ataxia: A Systematic Review

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Abstract
The effectiveness of exercise and physical therapy for children with ataxia is poorly understood. The aim of this systematic review was to critically evaluate the range, scope and methodological quality of studies investigating the effectiveness of exercise and physical therapy interventions for children with ataxia. The following databases were searched: AMED, CENTRAL, CDSR, CINAHL, ClinicalTrials.gov, EMBASE, Ovid MEDLINE, PEDro and Web of Science. No limits were placed on language, type of study or year of publication. Two reviewers independently determined whether the studies met the inclusion criteria, extracted all relevant outcomes, and conducted methodological quality assessments. A total of 1988 studies were identified, and 124 full texts were screened. Twenty studies were included in the review. A total of 40 children (aged 5–18 years) with ataxia as a primary impairment participated in the included studies. Data were able to be extracted from eleven studies with a total of 21 children (aged 5–18 years), with a range of cerebellar pathology. The studies reported promising results but were of low methodological quality (no RCTs), used small sample sizes and were heterogeneous in terms of interventions, participants and outcomes. No firm conclusions can be made about the effectiveness of exercise and physical therapy for children with ataxia. There is a need for further high-quality child-centred research.

Keywords Exercise · Physical therapy · Paediatrics · Ataxia · Systematic review

Introduction

Ataxia is a common childhood movement disorder, with an estimated worldwide prevalence of 26/100,000 for both genetic and acquired causes [1]. Ataxia is most frequently caused by damage to or dysfunction of the cerebellum and its associated connections, and this is termed cerebellar ataxia. The primary features of cerebellar ataxia include reduced limb coordination (for example, dysmetria and tremor), postural and gait deficits, problems with oculomotor control and dysarthria [2]. Sensory ataxia refers to dysfunction of the proprioceptive input from the periphery and the ascending systems [3]. Sensory ataxia can disrupt limb co-ordination and, particularly, gait, depending on the site and size of lesion [4]. Ataxia may result in a range of functional difficulties involving balance and walking, reaching, grasping and manipulation, eye movement, swallowing and speech intelligibility [5, 6]. Childhood ataxias may be acquired (e.g. following stroke, traumatic brain injury (TBI), cerebral palsy (CP), cerebellar tumour), inherited (e.g. spino-cerebellar ataxia (SCA), Friedreich's ataxia (FRA)) or idiopathic [2]. In the absence of effective pharmacological options, rehabilitation, particularly, physical therapy, remains the mainstay of treatment [7–9].

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Eight literature reviews have previously reported on the effectiveness of rehabilitation (typically focused on physical therapy and exercise interventions) for primarily adults with ataxia [10–17]. A detailed analysis of these eight reviews was undertaken to determine whether a new systematic review that focussed exclusively on children with ataxia would add to knowledge to this field. The results of this analysis indicated that none of the reviews comprehensively searched for studies that included children or clearly reported the effect of interventions on children. Five reviews identified either one [12, 14, 16, 17] or two [15] studies that involved children; one review included one study that involved participants aged 17–69 years [11]; one review did not identify any studies involving children [13]; and one expressly focussed on adults [10]. None of the reviews that identified studies involving children discussed the results separately from studies involving adults. Furthermore, five reviews only included studies about people with a degenerative ataxia [11–13, 16, 17], and three reviews included people with ataxia presenting as part of another condition such as multiple sclerosis [10, 14, 15].

Studies involving children and young people with ataxia may have been omitted from these published reviews due to limitations in the search methods and restrictions placed on inclusion criteria which varied considerably (Table 1).

Concerns about the lack of high-quality studies were raised by the review authors, but, overall, emerging evidence of the effectiveness of rehabilitation interventions was reported for adults living with a progressive ataxia [12, 13, 16, 17], and other causes of ataxia [10, 14, 15]. However, interventions that show promise with adults will not necessarily have the same impact with children and young people for several reasons.

Brain development continues throughout childhood as increasingly more sophisticated movement repertoires are acquired through experience-based learning [18]. Normative data derived from the International Cooperative Ataxia Rating Scale (ICARS) (a scale which quantifies the level of ataxia impairment), for example, has shown that typically developing children only approach their "adult norm" score of zero (indicating no coordination problems) at approximately 12 years of age [19]. Children's central nervous systems may therefore respond differently to rehabilitation interventions when compared to a mature but similarly impaired adult system. Age is likely to affect engagement and compliance with the chosen modality or intervention and may impact the targeting and timing of rehabilitation efforts. Children have different information-processing capacities compared to adults and respond differently to motor learning and skill-acquisition paradigms, suggesting children may require more exercise practice time before learning is consolidated when compared to adults [20]. Certain cerebellar pathologies are more prevalent in children, e.g. midline floor of the fourth ventricle tumours are common in children, whereas many of the SCAs emerge only in adulthood. These different pathologies impact cerebellar function in different ways and may require different rehabilitation strategies. As none of the review authors searched specifically for studies with children, or focussed on, or reported interventions or outcomes for children and young people with ataxia, the overall picture of research in this field is not well understood. An up-to-date and comprehensive assessment of the evidence is required to develop a better understanding of, firstly, the effectiveness of exercise and physical therapy interventions for children and young people with ataxia and, secondly, the different types of interventions that have been investigated to date.

Table 1 Limitations of existing reviews of the evidence

Study	Limitation
Marquer et al. [15]	Narrative review, no clear search date or search strategy. Focussed on describing the assessment and treatment of postural disorders.
Synofzik and Ilg et al. [16]	Included only prospective studies using high-intensity training schedules and outcomes addressing gait and stance.
Trujillo-Martín et al. [11]	Included only studies with a minimum of three participants and a minimum 6-month follow-up period.
Martins et al. [13]	Included only studies published since 2000 and which scored at least five out of ten on the Physiotherapy Evidence Database Scale (www.pedro.org.au/).
Artigas et al. [12]	Used broad search terms but did not report inclusion criteria.
Fonteyn et al. [14]	Children were included but only prospective clinical trials, and case studies were included in the review if at least two different studies used the same intervention.
Milne et al. [17]	Included children and prospective and retrospective studies of randomised and non-randomised controlled studies and cohort studies, but not case studies or case series

Description of the Interventions

Exercise is defined as "physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (p. 128) [21]. Exercise may improve the following components of physical fitness: muscle strength, muscle endurance and cardiorespiratory fitness. Exercise interventions may be categorised as resistance training or aerobic (endurance) training based on the component of fitness the exercise programme is targeting. Resistance (strength) training is defined as the body's muscles working or holding against an applied force. Body weight, free weights, machine weights and elastic bands may be used to apply force [22]. Aerobic training comprises the body's large muscle groups moving in a rhythmic manner over a sustained period of time [22]. Examples of aerobic exercise include walking, running, cycling and arm ergometry. Endurance training or cardiovascular training is a type of aerobic training that includes activities that increase breathing and heart rates. Exercise programmes may target muscle strength, muscle endurance or cardiorespiratory fitness or a combination of these components described as "mixed training" [23].

Physical therapy aims to restore movement and function following injury, illness or disability using movement, exercise and manual therapy, as well as education and advice [24]. Physical therapy may include exercises as described previously and/or the following: task-specific training with the aim of (re)acquiring a motor skill (with or without using robotic exoskeletons); exercises that focus on regaining or sustaining control of the proximal muscles of the trunk, shoulder and pelvic girdle; exercises that aim to improve static and dynamic balance and proprioception as a component of postural control; and stretching exercises that aim to improve range of movement. Adjuncts, such as treadmill training with or without partial body weight support, functional electrical stimulation of voluntary muscles and exergames that use computer technologies to provide an interactive environment which requires limb movement to react to on screen game play (e.g. Wii, X Box), may also be included as part of a physical therapy training programme.

Neuroscientific and Theoretical Foundations for Interventions

As part of a distributed system, the cerebellum plays a key role in motor control and motor learning [25, 26], and, for this reason, it was customary to believe that interventions to improve motor function for people with ataxia would be ineffective [27]. Recent evidence suggests that although adaptive learning is affected by cerebellar damage [28], motor learning is possible despite cerebellar pathology [29, 30]. Sparing of the deep cerebellar nuclei and the extracerebellar systems is thought to be a factor in recovery of motor function in children following cerebellar injury [28].

Contemporary rehabilitation approaches for people with cerebellar dysfunction may involve strategies that compensate for the underlying impairment, e.g. increasing inertia by weighting equipment, such as walking aids, or weighting the ataxic limb or strategies that aim to improve or restore function by treating cerebellar-specific impairments, e.g. through balance and ocular training [31]. The potential mechanisms underlying the restorative and compensatory approaches are the subject of ongoing investigations (see, for example, Bhanpuri et al. [32]). It is also possible that exercise interventions, as defined previously, may increase physical fitness and physical activity levels and deliver health-promoting effects. Exercise interventions may also confer benefits that reside outside of the biomedical sphere by having a positive effect on a child's well-being and life experience. These broader outcomes are considered essential to understanding childhood disability and should be incorporated in research protocols [33].

The aims of this systematic review were to map and critically evaluate the type, range, scope and scientific quality of exercise and physical therapy interventions on impairment, function, participation and quality of life for children and young people with ataxia. The results of this review aim to inform healthcare professionals about the effectiveness and quality of the evidence for these interventions and to assist the development of future research in this field.

Methods

The PICO (population, intervention, comparisons and outcomes) framework was used to develop the literature search strategy.

Types of Studies

All prospective and retrospective intervention studies where before and after outcome data were collected, such as randomised controlled trials, quasi-randomised controlled trials, non-randomised studies and single-case experimental designs, were included. Case studies were included if measures of outcome were reported. Case reports and case descriptions where the impact of an intervention was not determined, and where no measures of outcome were reported, were excluded from the review.

Participants

Children and young people 18 years old or under, of any functional ability, with ataxia as the primary impairment were eligible. Studies that included participants who were under 18 years as well as those over 18 years of age were categorised

as "mixed aged group" studies and were included in the review but reported separately. If data from participants at or under 18 years old could be extracted from these "mixed age group" studies, these data were reported separately.

Participants with ataxia as a result of posterior fossa tumour, stroke, CP, brain injury, idiopathic cerebellar ataxia, autosomal-recessive ataxia (e.g. FRA; early-onset ataxia, such as ataxia telangiectasia (AT); adolescent-onset ataxia) or autosomal-dominant ataxia were included. Studies where participants had other childhood conditions, where ataxia is a feature but is not the primary motor impairment (e.g. Angelman's syndrome, Wilson's disease), were excluded. Participants with other conditions known to affect the cerebellum but with other primary signs and symptoms, such as developmental coordination disorder and autism, were also excluded. Studies that included participants with ataxia as a result of self-limiting conditions that usually resolve (e.g. some types of acute neurotoxicity or infection) were excluded.

Types of Interventions

Studies using or describing the following exercise, training and physical therapy interventions were included:

a) Exercise interventions that aimed to improve one of the following components of physical fitness, i.e. muscle strength and/or muscle endurance and/or cardiorespiratory fitness and may include, for example, resistance training and/or aerobic training exercises
b) Physical therapy interventions that aimed to improve co-ordination and/or dexterity and/or balance and/or posture
c) Exercise interventions or physical therapy interventions that used exercise devices, such as treadmills, body weight support systems and robot-assisted exercise protocols to improve a component of physical fitness and/or co-ordination and/or dexterity and/or balance and/or posture
d) Exercise interventions or physical therapy interventions that involved riding horses or mechanical horses, exercises in water, including swimming, to improve a component of physical fitness and/or co-ordination, and/or dexterity and/or balance and/or posture
e) Physical therapy interventions that aimed to improve physical functioning through task- or part task-specific practice, e.g. constraint-induced movement therapy (CIMT)
f) Physical therapy interventions described as "Bobath" or neurodevelopmental therapy (NDT)
g) Functional electrical stimulation (FES) and/or neuromuscular electrical stimulation (NMES) and functional orthoses, such as Lycra garments, and upper and lower limb splints, were only included if the intervention was used in conjunction with exercise interventions or physical therapy interventions (reflecting conventional practice) or as a comparison to exercise interventions, as defined previously, to improve one of the components of physical fitness or co-ordination, dexterity, balance, posture or function.

The following interventions were excluded because they were not considered to be exercise or physical therapy interventions: psychological interventions, interventions restricted to improving communication (speech or other means of communication) or swallowing, breathing exercises, acupuncture, vibration therapy or types of non-invasive brain stimulation (in isolation or combined with exercise interventions).

Comparisons of interest (where study design permitted) were exercise and physical therapy interventions (as described previously) versus no treatment, or usual care, or a comparison of one exercise or physical therapy intervention with another exercise or physical therapy intervention.

Outcome Measures

As there are no gold standard outcome measures for children with cerebellar ataxia, the following outcomes were indicative and not specified as inclusion criteria for this review.

Primary Outcomes

1. Activity defined as a person's ability to execute a task [34]. Primary outcomes may focus on completing activities of daily living and application of skills within a range of different settings (e.g. the community/home/school/primary or secondary care setting). For example, the Gross Motor Function Measure [35] and WeeFIM [36].
2. Participation defined as a person's involvement in a life situation [34]. For example, the Paediatric Evaluation of Disability Inventory [37].
3. Health-Related Quality of Life (HRQoL) defined as the impact of disease and treatment on physical, psychological and social domains of health as distinct areas that are influenced by a person's experience, beliefs, expectations and perceptions [38, 39]. For example, the Child Health Questionnaire [40]. The incidence and nature of adverse events, such as injury and delayed-onset muscle soreness, where reported.

Secondary Outcomes

Body functions and body structures defined as changes in physiological systems or in anatomical structures [34], for example, muscle strength, endurance, fatigue, pain, cardiorespiratory fitness, balance, ataxia severity and coordination. For example, the Scale for the Assessment and Rating of Ataxia [41].

Any measure that purported to measure these outcomes was included, regardless of whether or not it was validated specifically for children with ataxia.

Outcomes were collected for the following time points: short term (0 to 1 month post-intervention), intermediate term (> 1 month to 6 months post-intervention), and long term (> 6 months post-intervention).

Search Methods for Identification of Studies

The following databases were searched from inception to February 2018: Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), CINAHL (EBSCOhost), ClinicalTrials.gov, EMBASE (OVID), Ovid MEDLINE, Physiotherapy Evidence Database (PEDro) and Web of Science (all databases). The conference proceedings of the International Society for Paediatric Oncology (SIOP), the International Symposium on Pediatric Neuro-oncology (ISPNO) (2005–current) and the World Confederation for Physical Therapy (WCPT) were also included.

The search terms child* OR pediatric OR paediatric OR adolescent OR infant were combined with results from a second search for the terms ataxi* OR atax* OR co-ordination OR "motor impairment" OR "balance impairment" OR "postural instability", and these results were combined with results from the third search for "physical therapy" OR "physiotherapy" OR "rehabilitation" OR exercise OR "exercise therapy" OR "physical activity" OR "home exercise programme" OR "balance training" OR "postural training" OR "co-ordinative training" OR "hydrotherapy" OR "aquatic therapy" OR "neurodevelopmental therapy" OR "strength training" OR "muscle strengthening" OR "virtual training" OR "treadmill training" OR "kinesiology taping" OR "lycra". This search strategy was adapted as appropriate for each source. Limits were not imposed on searches for language, date or publication status. The reference lists of included studies and relevant systematic reviews identified with the search results were also searched.

Selection of Studies

Two review authors (HH and EC) independently screened the titles and abstracts of the search results and excluded studies that did not meet the search criteria. Where studies appeared to meet the inclusion criteria, or where there was any doubt about inclusion, the full text of the published paper was retrieved. Two review authors (HH and EC) independently reviewed these papers against the inclusion criteria. Any disagreements regarding the exclusion of studies, at any stage of the review process, were resolved through discussion. Where an agreement about inclusion or exclusion could not be reached, a third review author (LB) made the final decision.

Data Extraction and Management

Two review authors (HH and EC) extracted data independently. Disagreements about the extraction of data were resolved by discussion. If a resolution was not reached, a third review author was consulted (LB). (The data extraction checklist is available as Supplementary material). The following information was extracted where possible:

- Authors, title, abstract, publication type, publication record, country of origin
- Study design
- Sample size
- Study population: sex, age, ethnicity, diagnosis, type of ataxia and gross motor function, where sufficient information was provided. Walking function was recorded, where possible, as unaided walking, walking with aids or unable to walk, and according to other validated measures, e.g. Gillette Functional Assessment Questionnaire [42]. Ataxia severity was recorded where possible, e.g. Scale for the Assessment and Rating of Ataxia (SARA) [41] and Brief Ataxia Rating Scale (BARS) [43].
- Intervention: aim of the intervention, type of exercise programme (e.g. aerobic exercise), mode of delivery (e.g. home programme), type(s) of location(s) where the intervention occurred (including any necessary infrastructure or relevant features), supervised or unsupervised programme, exercise mode (e.g. cycle ergometry, treadmill), exercise dose (i.e. duration, intensity, and frequency of exercise), tailoring/modification of the intervention to an individual (what, why, when, how), duration of programme.
- Intervention provider: profession, expertise, background, specific training received.
- Compliance: fidelity (whether the intervention was delivered as intended) and adherence to the prescribed dose (frequency, intensity, duration); how and by whom this was assessed.
- Outcome measures.
- Results: short term (0 to 1-month post-intervention), intermediate (greater than 1 month to 6 months post-intervention), and long term (> 6 months post-intervention) follow-up.
- Adverse effects.
- Conflicts of interest, declarations of conflicts of interest and sources of funding.

The methodological quality of the included studies was appraised using the Oxford Centre for Evidence-Based Medicine (OCEBM) level of evidence classification [44] (Table 2). This appraisal method is consistent with other internationally recognised guides. Where disagreements could not be resolved through discussion between HH and EC, a final decision was made by a third author (LB).

Table 2 Oxford Centre for Evidence-Based Medicine 2011 levels of evidence

Level of evidence	
Level 1[a]	Systematic review of randomised trials or *n*-of-1[b] trials
Level 2[a]	Randomised trial or observational study with dramatic effect* (*level may be graded down on the basis of study quality, imprecision, indirectness, etc.)
Level 3[a]	Non-randomised controlled cohort or follow-up study
Level 4[a]	Case series, case–control studies or historically controlled studies.
Level 5	Mechanism-based reasoning

[a] Level may be graded down on the basis of study quality, imprecision, indirectness, inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size.

[b] Definition of *n*-of-1 trial: a variation of a randomised controlled trial in which a sequence of alternative treatment regimens is randomly allocated to a patient. The outcomes of regimens are compared, with the aim of deciding on the optimum regimen for the patient

Results

Type, Range, Scope and Methodological Quality of Selected Studies

After the removal of duplicates, 1927 studies and 16 conference abstracts were screened. Following screening, 124 full-text studies were assessed for eligibility. Of these, 56 were excluded as they did not involve children, 24 did not have ataxia as the primary diagnosis/presenting feature and 22 did not meet the intervention criteria stated in the search strategy. Two studies could not be obtained [45, 46]. Twenty studies were included in this review. All studies were published in the last 20 years (1999–2017), with ten in the last five years. The PRISMA flow diagram [47] is presented in Fig. 1.

A total of 40 children with ataxia as a primary impairment participated in the studies included in this review. Where stated, the ages of the children with ataxia ranged from 5 to 18 years (median 13 years). Where stated, the duration of the intervention ranged from 2 weeks [48] to 19 months [49] (median 7 weeks) and intensity ranged from 10 min [48] to 2 h per session [50] (median 45 min per session). Frequency ranged from once every three months [51] to six days per week [48] (median 3 sessions a week), excluding an outlier where Lycra garments were prescribed daily for six weeks, for 6 h a day plus usual physical therapy care for 10–30 min per day [52].

Studies Involving Mixed Groups Where Data from Children with Ataxia Could Not Be Extracted

Nine of the included studies comprised mixed groups of participants, either children with adults or children with ataxia with children with other primary impairments. Data from the children with ataxia in these studies could not be extracted for this review. Five studies with children with cerebral palsy, with sample sizes ranging from 8 to 70 participants, included one [50, 53], two [54], three [55] or six [56] participants with ataxia as their primary impairment. The methodological quality of these studies was judged at OCEBM level 3 for an RCT [50] downgraded from level 2 due to increased risk of bias for being underpowered and OCEBM level 4 for four single group (before and after) studies [53–56]. The results from participants with ataxia in these studies were not reported separately from the group results, and, therefore, the data were not able to be extracted or included in this review. Interventions included the following: NDT vs Adeli Suit Treatment (training of gross motor function whilst wearing an externally fitted suit which provided stability and resistance) [50], strength training [53], NDT [54], aerobic treadmill training [55] and robot-assisted gait training [56]. Biffi et al. [57] conducted an OCEBM level 4 before and after trial, to investigate the efficacy of an immersive virtual reality platform to enhance walking ability in children with acquired brain injury. One child with ataxia was included in a total sample of 12 children. Significant improvements were reported in gross motor function, endurance (6MWT) and autonomy in daily life. Overall, small and predominantly short-term benefits were reported in this group of studies which cannot be used to draw conclusions about the effectiveness of these interventions for participants with ataxia.

Of the remaining three studies in this group, Nardone et al. [58] included one young person aged 16 in an otherwise adult sample of 27 participants with cerebellar dysfunction caused by either degenerative disease or cerebellar stroke, in an OCEBM level 4, single group (before and after) study. Small short-term positive effects in both groups were reported on body sway and gait parameters and the FIM (Functional Independence Measure) following a balance and gait training protocol. Sabel et al. [59] conducted a randomised cross-over trial (downgraded from OCEBM level 2 to level 3 due to increased risk of bias for being underpowered) that compared active video gaming and coaching with usual care in a group of 13 children following treatment for brain tumour. Four of the cohort had posterior fossa tumours. The results demonstrated that the home-based intervention was

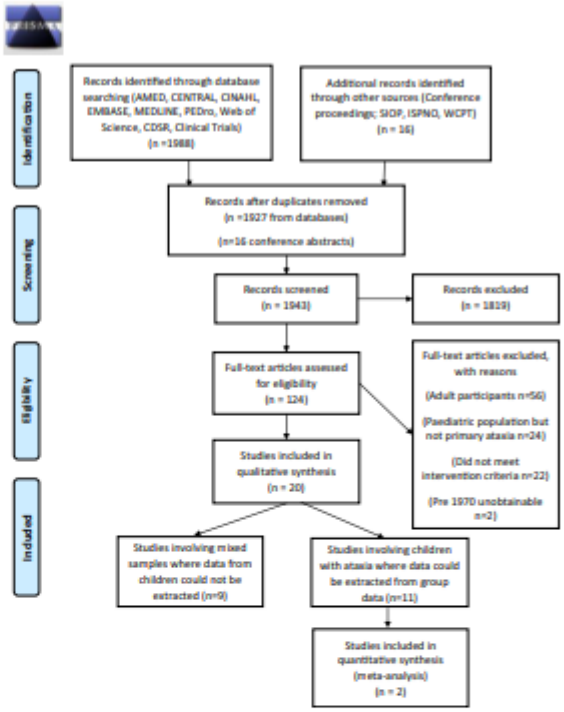

Fig. 1 PRISMA flow diagram: search results

feasible and improvements in body coordination were reported using the BOT2 (Bruininks-Oseretsky Test of Motor Proficiency). Santos et al. [60] included one child aged 15 years in an otherwise adult group of 28 people with SCA in an OCEBM level 4 prospective (before and after) feasibility trial of virtual reality balance training. Improvements were reported in balance and quality of life measured using the Berg Balance Scale, Dizziness Handicap Inventory and the SF-36 (Short-Form—36; a patient-reported outcome measure). None of the data for the children with ataxia in these studies were reported separately, and, therefore, no conclusions could be drawn about the effectiveness of the intervention for these participants.

Studies Involving Children with Ataxia Whose Data Could Be Extracted

The remaining eleven studies (summarised in Table 3) involved children with ataxia whose data could be extracted for this review [48, 49, 51, 52, 61–67]. Schatton et al. [66] included data from one participant previously reported in the $n = 1$ pilot study conducted by Synofzik et al. [67]. In the following summary, data from this child have only been counted once. The studies included here were conducted mainly in North America ($n = 4$), with additional contributions from Australia, Brazil, Germany, New Zealand and the United Kingdom. This group of studies included a total of 21 children, aged 5 to 18 years; eleven boys and nine girls (one paper did not state gender), with progressive ataxia ($n = 14$), ataxic CP ($n = 3$), cerebellar/brain stem infarct ($n = 1$), traumatic brain injury ($n = 1$), cerebellar tumour ($n = 1$) or a non-progressive cerebellar ataxia ($n = 1$).

Five studies provided balance, coordination or dexterity training [48, 62, 64, 66, 67]; three provided mixed training, classified as conventional physical therapy [49, 51, 65], one provided aerobic treadmill training [61], one provided horse-riding training [63] and one provided a full-body Lycra suit in addition to usual care [52].

The duration of the intervention ranged from 2 weeks [48] to 19 months [49] (median 12 weeks). Where stated, intensity

Table 3 Data extraction for the eleven main studies

Study	Study design	Participants				Intervention	
		Age/sex	Size	Diagnosis	Functional level	Description	Dose: duration, frequency, intensity
Ada et al. [48] Australia	SCED (ABA design)	5-year-old female	$N = 1$	Cerebellar tumour (low grade) resected 3.5 years previously.	Reported UE coordination problems.	Dexterity training using a computerised tracking task on a computer.	2/52, 12 sessions, 10′
Cernak et al. [61] USA	Case report	13-year-old female	$N = 1$	Cerebellar ataxia post-brain haemorrhage (16/12 previous).	Non-ambulatory.	Partial body weight-support treadmill training with over-ground practice.	4/52, 5×/wk, 40′. GAP 1/12. Then 4/12, 5×/wk, 30′
Da Silva and Iwabe-Marchese [62] Brazil	Case report	12-year-old male	$N = 1$	Ataxic CP	GMFCS level II	Video gaming targeted at balance using the Wii (with balance board).	4/12, 3×/wk 30′. Total 40 sessions
Frank et al. [63] USA	Case report	6-year-old female	$N = 1$	Ataxic cerebral palsy	Ambulatory GMFCS level I	Hippotherapy	8/52, 2×/wk, 45′ (16 Rx sessions)
Harris-Love et al. [51] USA	Case report	14-year-old female	$N = 1$	FRA	Walking frame and powered wheelchair for mobility. Assistance of 1 to stand.	PT and adapted PE inc; bimanual task-, task-orientated training, strengthening, stretching, gait training using a walking aid.	1×/month, 60′ (school) for 12/12, plus × 1/quarter 60′ (PT dept.), plus 20–30′ daily adapted PE, plus HEP, 5×/wk
Ilg et al. [64] Germany	Before/after, no control group (intra-individual control design)	Age 11–20. 5 male, 5 female	$N = 7/10 \leq 18$ years old	Children with spinocerebellar ataxia. 2–17 years post-diagnosis	SARA score 7–13.5	X Box coordinative training.	2/52, 4×/wk, 60′. Then, 6/52, varied intensity; 20–175′ per wk.
Mulligan et al. [65] New Zealand	SCED (notal second intervention shorter) (ABCB design)	9 years old	$N = 1$	Non-progressive congenital ataxia.	Able to climb stairs without a rail. Modified TUGG (from the floor) at first assessment: 72 s.	Compared two PT interventions: Rx 1—strengthening pelvic/trunk musculature and practising midline in sitting and kneeling. Rx 2—challenge postural control in different positions with head mvts performed simultaneously to reduce amount of visual information.	11/52, 3×/wk, 30years GAP 5/52. Then 5/52, 3×/wk 30years
Nicholson et al. [52] UK	Before/after (measures on single occasion)	$N = 12$., ages 2–17. Male $n = 7$, female $n = 5$.	$N = 1/12$ child with ataxia	CP	Upper limb impairment	Lycra garment (continued to receive usual therapy during study period)	2 weeks initial gradual exposure, then 6 h per day for 6/52.
Sartor-Glittenberg and Bridaner [49] USA	Retrospective case report	$N = 3$ aged 16–22. One aged 16 with ataxia	$N = 1$ with ataxia	TBI (5/12 post).	Walked with a walking frame and maximum assistance of 2.	Mixed group PT and individual Rx. Activities to improve proximal stability, coordination and balance. Outpatient day programme. Also included climbing on an artificial wall in rock climbing gym.	77/52, 4-5×/ wk, weaned down to 1–2× wk.

Table 3 (continued)

Schatton et al. [66] Germany	Before/after, no control group (intra-individual control design)	Age 6–29. 7 male, 3 female	$N = 6/10 \leq 18$ years old	Children with SCA	SARA score 13–29	Exergame training. (Nintendo Wii® and Microsoft XBOX Kinect®)	Phase1: 1/52 lib, 4 × 60 min session then 5/52 at home. Phase2: 2/7 booster then 5/52 home training ×3 wk 45 min per session
Synofzik et al. [67] Germany	Case report	10-year-old male	$N = 1$	AT diagnosed at 3 years old	SARA score gait 7/8 (severe ataxia)	Video gaming coordinative training.	1/52 clinic, frequency and intensity not stated 2 update sessions. Then 5/52 home. Update then 6/52 home.

Study	Intervention Provider/setting	Outcome measures	Results Short term (ST) Intermediate term (IT) Long term (LT)	Compliance (fidelity and adherence)	Adverse effects	Oxford
Ada et al. [48] Australia	Home, supervised by parents	Finger to nose test, 9HPT	ST: 8% improvement in tracking. FNT and 9HPT improved but not significantly. IT and LT not reported.	Reported good adherence to the intervention.	Reported as not harmful	4
Cernak et al. [61] USA	PT dept. and home-based training (with rehab assistant)	Gillette, Functional Walking Scale, WeeFIM (transfers and mobility subscale), number of unassisted steps.	ST: Minimal change at 1/12. IT: At 6/12 Gillette improved to walking for household distances. Transfers improved from moderate assistance to modified independence. Walking improved from maximum assistance to supervision. No. of unassisted steps improved from 0 to 200 LT not reported.	19/20 sessions completed in clinic. Not reported for home training	Fatigue and discomfort from harness	4
Da Silva and Iwabe-Marchese [62] Brazil	Not reported. Setting unclear	GMFM-66, BBS, gait kinematics.	ST: BBS increased from 48 to 53 points, GMFM: no change in dimensions A–C; D increased from 64.63 to 65.33, dimension E increased from 72.63 to 81.98, the overall mean score improved from 71.69 to 77.46. Gait parameters: no change reported. IT and LT not reported	Not reported	Not reported	4
Frank et al. [63] USA	PT delivered Rx at the stables.	GMFM-66, PODCI, PSPCSAYC.	ST: GMFM 66, dimension D: no change (95) Dimension E improved from 87.5 to 93. PODCI improved significantly in 3 domains. PSPCSAYC	Number of sessions reported. HEP adherence reported.	Not reported	4

Table 3 (continued)

					scores on 2 of 4 domains improved by 2 points. IT: GMPM 66 D improved to 97.4, E improved to 94.4. PODCI improvement in 3 domains. PSPCSAYC minimal change. LT not reported			
Harmsen-Louvet et al. [51] USA	PT dept., school and home	9HPT, SLST, manual muscle testing, passive ROM, gait speed, DLST, step length asymmetry, step time asymmetry, self-report falls history.			ST: at 12/12 9HPT reduced (60.0 to 36.6 s), ROM static or improved. MMT declined SLST increased 2.7 to 2.9. Fall rate decreased (12 to 3.) Gait speed varied depending on walker type. IT and LT not reported.	Not reported	Not reported	4
Ilg et al. [64] Germany	Lab-based training supervised, followed by home-based training.	SARA, Dynamic Gait Index (DGI), motion analysis (leg placement), ABC scale (balance confidence) measured at baseline, pre-treatment, post 2 weeks lab training, post 6 weeks home training.			ST: significant improvement in SARA (~2 on average) and DGI. Improvements in lateral sway and error during leg placement task. Non-significant improvements reported in ABC. IT and LT not reported.	Noted training intensity correlated with improvement in SARA posture subscore.	Not reported	3
Mulligan et al. [65] New Zealand	Rx 1: PT in school Rx 2: researcher, setting unclear	Modified TUGG GMPM, GMPM, timed independent stair climbing.			ST: mTUGG improvement of 35 s (from first intervention to 5:52 post end of 2nd intervention). GMPM overall improvement from 81 to 96% at end Rx 2. GMPM not clearly reported (graph compared to repeated results). Timed stair climbing improvements reported with and without a rail. Reported better maintenance of results at end of second treatment block. LT not reported	Not reported	Not reported	4
Nicholson et al. [52] UK	Mostly home setting (not supervised)	PEDI, reach and grasp (motion analysis), self-devised parent questionnaire re practicalities of the Lycra garment.			ST: improvements in PEDI self-care +8, mobility +4, social domains +7. No change in PEDI care giver assistance score. Improved trunk stability and upper limb function reported. Parental questionnaire not reported. IT and LT not reported.	Group but not individual daily use of the garment reported.	Impaired functional mobility, discomfort. Found uncomfortable to crawl in suit	4
Sartor-Glittenberg and Bricker [49] USA	Supervised with PT.	Muscle strength (0–5 scale), coordination (timed heel to shin, toe taps), BBS, SLST, FES, 6MWT, participation in activities via interview and observation.			ST: Increased lower limb strength, improved co-ordination in both LEs, BBS improved from 4 to 23, SLST improved from 0 to 3.5 s (R), 0 s to 1.5 s (L), FES improved from 37 to 95, 6MWT improved from 61 to 259 m. IT and LT not reported.	Not reported re therapy sessions, diary to HEP completed	Not reported	4

Table 3 (continued)

Schatton et al. [66] Germany	Lab-based training supervised, followed by home-based training	SARA, GAS, Romberg sitting task. Measured at baseline, pre-treatment, after phase 1, after phase 2.	ST: significant improvement in SARA (− 2.5 on mgel. Higher GAS. Reduced body sway. IT and LT not reported.	Noted training intensity at home correlated with improvement in SARA	Not reported	3
Synofzik et al. [67] Germany	PT (lab-based) and home-based	SARA, GAS, sway in sitting	ST: no change between 2 baseline phases. End of intervention SARA improvement of 4 points. GAS standing + 2, sitting + 1. Mvt analysis: less sway in sitting. 2nd baseline to end of intervention. IT and LT not reported.	Not reported	Not reported	4

Abbreviations not appearing elsewhere: PE, physical education; HEP, home exercise programme; /52, per week; /12, per month; Mvt, movement; Rx, treatment; SLST, single-leg stance test; FES, falls efficacy scale; DLST, double-limb support time; LE, lower extremity; SCA, spinocerebellar ataxia; UE, upper extremity; Wk, week; AT, ataxia telangiectasia

anged from 10 [48] to 60 min per session [51] (median 37.5 min per session). Frequency ranged from once every three months [51] to six days per week [48] (median 3 sessions a week), excluding Nicholson et al. [52], where Lycra garments were prescribed daily for six weeks, for 6 h a day plus usual physical therapy care for 10–30 min per day.

Nine of these studies were judged as OCEBM level 4 evidence; five single case reports [51, 61–63, 67], one case series [49], two single case experimental designs [48, 65] and one single group (before and after) design [52]. Two before and after studies with intra-individual comparison, blind assessment and extended baselines were elevated to OCEBM level 3 evidence [64, 66].

The Joanna Briggs Institute checklist for case reports was used to evaluate the quality of the case reports and the case series ($n = 6$) [68]. The two single case experimental designs (SCEDs) were evaluated using the CONSORT agreement for the reporting of $n = 1$ trial [69]. Studies categorised as before and after trials ($n = 3$) were evaluated using the NIH quality assessment tool for before–after (pre–post) studies with no control group [70]. The separate evaluation of the methodological quality of these eleven studies identified comparable strengths and limitations. For this reason, the results of the critical appraisal of this group of studies were considered together.

Characteristics, such as age, gender, diagnosis and genetic details (where relevant), were consistently reported but varied in the amount of detail offered. Psychosocial details were provided in one study [49]. Imaging results were reported by Sartor-Glittenberg and Brickner [49] and in supplemental information by Synofzik et al. [67]. Ataxia severity was rarely described in detail and only measured using a specific ataxia scale (SARA) in three studies from the same research laboratory [64, 66, 67]. Gross functional capacity was classified in four studies using the Gross Motor Function Classification System (GMFCS) [62, 63], the Gillette Functional Walking Scale and WeeFIM [61] or the Paediatric Evaluation of Disability Inventory (PEDI) [52]. Walking ability was described but not consistently measured in all relevant studies. Interventions were well-described, and the duration, frequency and intensity (dose) were consistently reported across all studies. Decisions about the prescribed dose of the intervention were not justified with respect to relevant theories or the results of other studies. Compliance was not consistently reported, particularly for home-based exercise programmes. Three studies identified primary outcomes [61, 64, 66]. Five studies reported measurement properties (validity and reliability) for one or more outcomes [49, 52, 61, 63, 65]. Only one study measured participation and quality of life outcomes [63]. All studies reported short-term outcomes (0 1 month post-intervention). No long-term outcomes were reported. Assessor blinding was reported in four studies [48, 64, 66, 67]. Adverse events were not routinely reported. One study

reported that the intervention was not harmful [48], and one study clearly reported harmful effects [52]. None of the included studies reported involving children and/or parents in the design or evaluation of the intervention.

Effectiveness of the Interventions

In the following evaluation, minimal detectable change (MDC) and minimal clinically important difference (MCID) scores have been provided where available to facilitate judgement of the reported effectiveness of interventions. Where paediatric data are not available, adult data have been used to provide proxy comparisons.

Conventional Physical Therapy

Three papers reported the effects of conventional physical therapy. Harris-Love et al. [51] used bimanual task practice, task-orientated training, stretching, strengthening and gait training using walking aids with a 14-year-old child with FRA. The intervention was provided once every three months over a 12-month period (60 min per visit) and continued as a home exercise programme five times a week. Monthly school-based physical therapy continued (60 min per session) plus school-based physical education (20–30 min per session, up to five times per week). The additional intervention equated to an extra 4 h of hospital-based physical therapy plus the home exercise programme, five times per week over a 12-month period. The improvement of 3.4 s on the 9-hole peg test (9HPT) was not considered clinically meaningful; however, a reduction in the number of falls from 12 to 3 falls per month (self-report) in the context of a measured deterioration in areas such as strength and gait speed may be considered a clinically significant change for a child living with a progressive condition.

Mulligan et al. [65] used a SCED (ABCB) with a child with non-progressive congenital ataxia (severity not reported), comparing strengthening and balance training (30 min, three times a week for eleven weeks) with interventions aimed to challenge postural control (30 min, 3 times a week for five weeks). Improvements were reported in the modified Timed Get Up and Go (TUG), Gross Motor Function Measure (GMFM), stair climbing and the Gross Motor Performance Measure. However, it was difficult to evaluate the separate effects of each intervention as multiple measures were not undertaken in each phase, standard SCED statistical analysis was not used and trends could be observed in the data from the A phase into the other phases.

Sartor-Glittenberg and Brickner [49] reported a retrospective case report of a 16-year-old boy in the subacute phase following TBI. Ataxia severity was not measured but was reported as severe. He required a walking frame and the maximum assistance of two people to walk short distances. A wide range of interventions were provided during 187 therapy sessions over 19 months. Improvements were reported for all outcomes. An improvement of 19 points in the Berg Balance Scale (BBS) exceeded the MDC of 5 points relevant for older adult clinical populations with an initial score of 0–24 points [71]. An improvement of 198 m in the Six-Minute Walk Test (6MWT) exceeded the MCID reported as relevant for adults with a range of medical conditions [72]. Motor co-ordination improved but did not reach age-equivalent norms.

Video Gaming and Computer-Assisted Training for Dexterity/Coordination and Balance

Five studies reported a positive effect of video gaming or computer-assisted training in children/young people with ataxia. As the participant in Synofzik et al. [67] was included in the data presented in Schatton et al. [66], only data from this second study are presented in this summary. Ada et al. [48] reported short-term but not statistically significant improvements in elbow dexterity (finger–nose test) and a timed upper limb task (9HPT) following a 2-week home programme of dexterity training for 10 min per day, using a computer-assisted elbow-tracking task (gravity eliminated), with a 5-year-old girl described as having severe upper limb ataxia following resection of a posterior fossa tumour. Da Silva and Iwabe-Marchese [62] reported immediate improvements following a 4-month programme of video game balance training (Nintendo Wii), in addition to usual care, for a 12-year-old boy with ataxic CP (GMFCS II—able to walk in most settings). A six-point improvement was reported in the GMFM-66 (exceeding the MCID for a large effect size reported by Oeffinger et al. [73]) and a five-point improvement in BBS (exceeding an MDC of four points relevant for older adults with an initial score of 45–56 points [71]). No improvement in gait kinematics was reported.

Ilg et al. [64] conducted an intra-individual control study using an eight-week video co-ordination-game training (X Box Kinect) programme (2 weeks in clinic (four 1-h training sessions) followed by 6 weeks at home) with 10 children and young adults ($n = 7 \leq 18$ years old) with an inherited progressive ataxia as their primary impairment (mean SARA 10.9, range 7–13.5). A mean group change reflecting a 2-point improvement in SARA (more than one point change would be considered a MCID for adults with a progressive ataxia [74]) and improvements in sway and leg placement were reported. Schatton et al. [66] reported a mean 2.5-point improvement in SARA scores (exceeding the one point MCID SARA change considered relevant for adults with a progressive ataxia [74]), at the end of a 12-week (1 week in clinic, 5 weeks at home, two update sessions and a further 5 weeks at home) video gaming programme (Nintendo Wii) using whole body-controlled commercially available games for ten participants ($n = 6 \leq 18$ years old) described as having advanced SCA.

Table 4 Comparison of change across time irrespective of age ($n = 20$)

	Time point 1	Time point 2	Significance
SARA median change over time (IQR)	13.5 (9.5)	11.5 (8.3)	$p < 0.001^a$

[a] Wilcoxon signed-rank test

IQR, interquartile range

As Ilg et al. [64] and Schatton et al. [66] used SARA as their primary outcome measure and provided data for all participants at all time points, data from these higher quality studies were pooled to conduct a meta-analysis of the effect of video game training on SARA scores. A comparison of change in SARA scores across time irrespective of age indicated a statistically significant and clinically meaningful reduction (improvement) in SARA scores from baseline to the end of the intervention (median reduction of 2 points, $p < 0.001$) (Table 4). A comparison of training time (overall dose) indicated that participants in Schatton et al. [66] spent a median of 160 min training compared to those in Ilg et al. [64] who spent a median of 70 min training (Table 5). This difference was statistically significant ($p = 0.03$), but the increased dose does not appear to have made a difference to outcome as measured by SARA, suggesting optimal dosages are yet to be determined. A comparison of change across time by age using pooled data from 13 children (≤ 18 years old) with pooled data from seven adults indicated that although SARA scores for children improved by a median of 0.5 points more than adults, the difference was not statistically significant ($p = 0.49$) (Table 6). Adults in these studies completed a median of 18 extra minutes of training compared to children, but the difference in training time was not statistically significant ($p = 0.49$) (Table 7).

Treadmill Training

Cernak et al. [61] conducted a single case study with a non-ambulatory 13-year-old girl with ataxia following a brain haemorrhage and reported functionally meaningful improvements in the Gillette Functional Walking Scale (from an initial score of 2 to a final score of 6—walks for household distances) and the WeeFIM mobility and transfer subscales. The intervention consisted of partial body weight-support treadmill training (in conjunction with over-ground walking practice) completed initially in the clinic setting (five days a week for four weeks) and then continued daily at home for further four months (five days a week).

Table 5 Comparison of training time irrespective of age

	Schatton et al. [66]	Ilg et al. [64]	Significance
N	10	10	
Median time (IQR)	159.9 (23.3)	70.5 (110.5)	$p = 0.03^a$

[a] Mann–Whitney *U* test

IQR, interquartile range

Hippotherapy

Frank et al. [63] reported short-term (eight weeks) and intermediate (two months) gains in GMFM dimensions D and E in a 6-year-old girl with mild ataxic cerebral palsy (GMFCS I—walks independently with limitations in speed, balance and coordination) following an eight week course of hippotherapy (16 sessions). Gains in the GMFM and the PODCI for global function, sports and physical function, and upper extremity and physical function exceeded the MCID for large effect sizes as interpreted by Oeffinger et al. [73]

Lycra Garments

Nicholson et al. [52] conducted a before and after study to investigate the effectiveness of wearing a Lycra garment (seven days a week, for six hours, for six weeks) and usual care (physical therapy home programme) on impairment and activity limitations with twelve children with CP, one of whom had ataxia and whose results were reported separately. The PEDI score (activity and participation levels) for this eight-year-old boy improved in self-care, mobility and social domains following completion of the intervention at six weeks. Improvements in proximal stability were reported, but the child was unable to crawl whilst wearing the suit and found it uncomfortable.

Discussion

The purpose of this systematic review was to evaluate the effectiveness of exercise and physical therapy interventions for children with ataxia. We also aimed to report the type, range, scope and scientific quality of relevant studies. Twenty studies involving 40 children with ataxia met the inclusion criteria. Nine studies included children with ataxia along with children with a number of other primary impairments/diagnoses or grouped children with adult participants. Data for the children with ataxia were unable to be extracted from these studies. The eleven remaining studies provided data from a total of 21 children with ataxia that could be extracted for this review. Our results suggest that only a small number of studies involving a very small number of

Table 6 Comparison of change across time by age

	Age 18 and under	Age 18 and over	Significance
N	13	7	
SARA median change over time (IQR)	2 (2.8)	1.5 (1.0)	$p = 0.49^a$

[a] Mann–Whitney *U* test

IQR, interquartile range

children with ataxia have been undertaken to investigate the effectiveness of exercise and physical therapy interventions for this population. The lack of RCTs suggests that research for children with ataxia is less well-developed than that for adults. Given that ataxia is a common childhood movement disorder [1] and exercise and physical therapy interventions are the mainstay of treatments available to these children [7], this result may be considered surprising.

The group of eleven studies considered in the main results for this review were of low methodological quality, consisting principally of single case reports and SCEDs. Overall, inconsistent descriptions and measurement of ataxia, poor reporting of adverse events, lack of long-term follow-up and the significant heterogeneity demonstrated in the type of intervention, age range, functional capacity, outcome measures and the duration, frequency, intensity and setting of the intervention limit the extent to which comparisons can be made across studies. Methodological and reporting limitations reduce the confidence with which conclusions can be drawn about the effectiveness of exercise and physical therapy interventions for children with ataxia. It was also observed that measures of fidelity were poorly reported thus making it difficult to understand if the interventions were practicable, acceptable to the children and their parents and able to be followed as intended.

This systematic review has revealed that research about the effectiveness of physical therapy and exercise interventions for children with ataxia is in a very early phase of its development and currently offers inadequate guidance about the efficacy of exercise and physical therapy interventions for children with ataxia. Nonetheless, the results of the studies reported here were on the whole promising and indicate that outcomes for this population have the potential to be improved through physical therapy and exercise. However, no firm conclusions could be drawn and no recommendations could be made based on the evidence reviewed. If the potential of these interventions is to be realised, stronger research designs that counter the limitations of the studies undertaken to date will be needed.

Table 7 Training time (minutes)

	Age 18 and under	Age 18 and over	Significance
N	13	7	
Median time (IQR)	132 (122.4)	150 (45.0)	$p = 0.49^a$

[a] Mann–Whitney *U* test

IQR, interquartile range

RCTs would make an important contribution to future research. However, recruitment issues and achieving relatively homogeneous samples may challenge the feasibility of running studies of sufficient size. Multi-centre studies and international collaboration might be needed to make these large-scale trials feasible. As an important first step, feasibility trials should be conducted before running fully powered RCTs. This would ensure that all the parts that make up the trial, including recruitment, randomisation, outcome measurement, adherence and compliance, proceed as intended [75] and are acceptable to the children and parents involved. Home-based training, for example, is likely to form a significant component of exercise interventions for children with ataxia [7]; however, Maring et al. [76] reported that although 73% of children with FRA were prescribed a home exercise programme, only 9% of these children carried out the programme as directed. An understanding of the acceptability of, and compliance with, interventions, over the short- and long-term, is critical to the development of RCTs. Potential problems with these programme components could be ironed out not only through running feasibility studies but also by involving children and parents in the design and planning of future studies and intervention programmes. SCEDs and *n*-of-1 trials, including prospective multiple cross-over and randomised case series designs, also offer valid alternatives to RCTs in situations challenged by heterogeneity and when large samples may be difficult to obtain [77]. Clear reporting of, for example, randomisation, primary outcomes, adverse events and blinding of assessors, should be included, and the CONSORT extension for reporting of *n*-of-1 trials [69] should be followed.

Children with ataxia may respond differently to physical therapy and exercise interventions when compared to children with other primary impairments [7] and when compared to adults with ataxia [64]. Involving children with different primary impairments (ataxia, spasticity, athetosis) or combining the data of children and adults in the same study, evident in twelve of the twenty trials that met the inclusion criteria for this review, should be reconsidered unless the potential effectiveness of the proposed intervention can be justified for all participants. If combining children with different pathologies and primary impairments in trials is considered a valid means of testing the efficacy of interventions, future studies should consider involving larger numbers of children with ataxia to enable a separate analysis to be undertaken so that conclusions can be drawn about the impact of

interventions for particular groups. Conducting separate studies for children with ataxia arising from a progressive condition to those for children with ataxia arising from a non-progressive form of ataxia seems reasonable, given the likely differing aims of the study, the different underlying pathological mechanisms that could affect the type of intervention used and the expected direction and meaning of responses to interventions. For example, the response to exercise interventions may differ for children with malignant posterior fossa tumours depending on the degree of damage to the dentate nuclei and the inferior vermis [78]. Children with conditions where lesions may be quite discrete are also likely to respond differently to exercise and physical therapy interventions when compared to children with more widespread involvement of the cerebellum, such as that found in progressive conditions [7]. These points stress not only the value of consistent and clear reporting of imaging results and lesion location in intervention studies but also the importance of giving further consideration to the length of follow-up and justifying the recommended dose. Key morbidities, e.g. visual and cognitive impairment, as well as measures of extracerebellar involvement (e.g. via the Inventory of Non-Ataxia Symptoms [79]), should also be reported to offer a more rounded account of a child's other impairments and a better understanding of the feasibility of delivering the intervention.

This review identified a diverse array of treatment interventions, with regard to the type, intensity, frequency, duration and setting. No justification was provided regarding decisions about dose. Although interventions are tailored according to individual need, these variations make it difficult to compare studies, to carry out meta-analyses, and to conduct replication studies. It is also difficult to examine the effect of usual care as well as other activities that children engage in as details are not always provided, and usual care may include, for example, strengthening, task-specific training, proximal control, balance and stretching exercises. This situation probably reflects the developing but incomplete scientific frame of reference underpinning exercise and physical therapy interventions for people with ataxia [7]. The broad range of interventions and the wide variation in dose, provided in all studies included in this review, may also reflect the lack of consensus about the best approach to take in this field of research. The high number of interventions using some form of technology in studies included in this review (seven studies published since 2012 used video game or virtual reality training programmes) also possibly highlights the potential for technology to drive interventions. These interventions usually include a home training programme which reduces the burden of attending hospital appointments and enables the intense and long-term training that might be necessary to achieve beneficial outcomes [7].

Rehabilitation is targeted at motor learning and adaptation, but it is not clearly understood if individuals with cerebellar dysfunction show similar learning-dependent neuroplasticity to that demonstrated in other areas of the injured brain. A greater understanding of neuroplasticity would provide a firmer foundation for developing exercise and physical therapy interventions to improve outcomes [80]. For example, future studies of exercise and physical therapy for children with ataxia would benefit from including brain imaging to help determine how the brain responds to training protocols of different intensities and may indicate whether neuroplastic changes occur in the cerebellum and/or other parts of the brain [7]. The results of these studies may help to tailor interventions by offering an understanding of the relationship between beneficial outcomes and the frequency, intensity and duration of the intervention. It would also be important to determine, for example, whether positive responses to interventions are related to improvements in ataxia-specific impairments or other training effects, such as improved strength or cardiovascular endurance and/or reduced pain, fatigue or falls, which were rarely measured in the studies included in this review.

Over forty different outcome measures were used in the twenty studies included in this review. The majority of measures focussed on balance and walking and gross motor function. Ataxia severity, dexterity and coordination were rarely reported. Some measures were reported as valid and reliable for children with ataxia. Only one study reported participation-level outcomes (PODCI and PSPCSAYC), and two studies used the PEDI which straddles activity and participation domains. A core set of standardised, valid and reliable measures operating at the impairment, activity and participation levels should be developed for future studies and to facilitate meta-analyses and should be incorporated into a reference group of agreed measures. The SARA and BARS are valid and reliable measures for determining the severity of ataxia in children with posterior fossa tumours [81], and paediatric normative values for the SARA are available [82]. A wide range of valid and reliable participation and well-being measures for paediatric healthcare have been developed (see, for example, Deighton et al. [83]) and should be incorporated into core sets. Data that has established norms for the progression of FRA is also now available (e.g. Friedman et al. [84]) and can be used for comparison to measure the effectiveness of interventions over the long-term and for calculating sample sizes.

Limitations

A comprehensive literature search was undertaken to identify studies concerning physical therapy and exercise interventions for children with ataxia. Although it is possible that some papers may have been missed, the search was wide-ranging and identified all the studies involving children reported in other reviews and additional studies that had not been previously reviewed. Full text screening was undertaken for a significant number of papers, as reported in Fig. 1, as it was not clear, through title and abstract screening, whether children were participants. Clearer use of indexing and key words

would therefore be of value to more easily identify studies for future systematic reviews as research in this field grows. As discussed in the results, we were unable to extract data from studies with mixed populations as the results from participants with ataxia were not reported separately. This meant that the overall reporting of results refers to a small number of children; however, this does reflect the limited number of studies with homogeneous patient groups and the small number of studies undertaken to date with children with ataxia.

Conclusions

This paper provides an up-to-date review of the literature regarding physical therapy and exercise interventions for children with ataxia. The results highlight the lack of rigorous research undertaken to date for this population, despite physical therapy interventions being a mainstay of treatment for this group of children. Key limitations of the reviewed studies included the following: small participant numbers, low methodological quality, heterogeneity in the nature of the populations and outcome measures used and lack of long-term follow-up. Positive short-term trends were reported in the reviewed studies, suggesting the tested interventions have potential therapeutic value. However, it is not possible to make formal recommendations for clinical practice based on the findings of this review.

The results of this systematic review indicate that high-quality, child-focussed studies are urgently needed. Results from RCTs with adults are not directly applicable to children, which adds impetus to the need to carry out further research with children. Ataxia significantly impacts children's access to education and participation in everyday activities and future life opportunities; it is, therefore, important to consider what would constitute optimal physical therapy-led interventions for this population.

Intervention studies should draw on theoretical principles, experimental neuroscience and motor-learning studies and other practical observations of what is likely to work in children with cerebellar damage. Feasibility studies should be undertaken before engaging in full-scale RCTs. Well-designed SCEDs with small groups of children may also help to test possible interventions and delivery configurations and would produce outcome measure data that could inform larger trials. Further attention to the development and testing of existing outcome measures for children, as well as consensus agreements about which measures should be used, would also strengthen trial design and facilitate comparisons across studies. Quality of life and participation measures should be recognised as a fundamental requirement. Where possible, imaging results should be reported. Parents and children should be involved in study design, and interventions (including type and delivery dose, as well as fidelity to protocols) should be clearly reported to allow efficacy and effectiveness to be determined. Multi-centre and international collaboration may be necessary to recruit sufficiently large samples for RCTs.

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Compliance with Ethical Standards

Conflict of Interest Helen Hartley, Elizabeth Cassidy and Lisa Bunn are chartered physiotherapists. As professionals who may be involved in the delivery of exercise interventions, it is plausible that they may be seen to have a bias favouring the effectiveness of exercise interventions. The authors confirm no other conflicts of interest.

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Appendix 4 – Summary of studies where data could not be extracted

Study	Study Design	Participants				Intervention			Outcome Measures	Results Short term (ST) Intermediate term (IT) Long term (LT)	Compliance (fidelity and adherence)	Adverse effects	Oxford
		Age/Sex	Size	Diagnosis	Functional Level	Description	Dose: duration, frequency, intensity	Provider/setting					
Bar Haim et al. (2006) **Israel**	RCT	Age 5-12. 17 male, 7 female.	N=12 NDT N=12 AST *1 child with ataxia in AST group	Children with CP	GMFCS level II/III/IV	Adeli suit (AST) and associated intervention vs NDT. 2 hours per day x5/7, x4/52	4/52, 2 hours per day, 5 days per week	Therapists trained in intervention	GMFM66, metabolic cost of stair climbing	ST: Data from child with ataxia not able to be extracted separately. At 1/12 both groups improved GMFM mean score. At 10/12 AST and NDT group higher than baseline. Mechanical efficiency improved in both groups at 1/12 + 10/12 but was only sig for AST at 10/12.	21/24 completed the 20 sessions within the 4 weeks	Not reported	3
Biffi et al. (2017) **Italy**	Before/After	Age 2-20.	N=12 *1 child was ataxic	Children with ABI	GMFCS level I/II	GRAIL system – an instrumented multi sensor platform based on immersive VR for gait training. Exercises tailored according to rehab goals.	3/52, 30 minute sessions, 4 times per week (10 sessions total)	Therapists trained in intervention	GMFM, Functional Assessment Questionnaire (FAQ), 6MWT, 3D gait analysis	ST: Data from child with ataxia not able to be extracted separately. Overall significant improvement reported in GMFM total score (especially dimension D and E), increased endurance on 6MWT and improved gait parameters.	Reported good compliance and enthusiasm for training	Not reported	4
Blundell et al. (2003) **Australia**	Before/ After (baseline, pre-test, post intervention and 2 months post)	Age 4-8. 7 male, 1 female.	N=8 * 1 child ataxic	Children with CP	All ambulatory	Mixed Group training included; stretches, treadmill walking, balance exercises, closed chain strength training.	4/52, 60 minutes x 1 per week	PT and parents to supervise session	Isometric tests, Motor assessment scale, 10m walk test and 9HPT	ST: Unable to extract data for participant with ataxia. Overall improvements in isometric (47%) and functional strength (150%). Increased gait speed (22%) and improved sit to stand performance.	All participants reported to have completed programme	Not reported	4

										Improvements retained at 8 weeks.			
Knox et al. (2002) **UK**	Before/ After (2 baseline measures, one immediately post, one 6 weeks post end intervention)	Aged 2-12. 9 male, 6 female.	N=20, *2 children ataxic. Full dataset N=15	Children with CP	GMFCS Level I-IV	Bobath based intervention	6/52, 75 minute x 3 per week for 16 sessions	Bobath trained therapists	GMFM, PEDI and family feedback. Assessment immediately post and 2 months post	Unable to extract data for child with ataxia. Overall significant improvements reported in GMFM total score, GMFM goal total, and PEDI self-care skills and PEDI care giver assistance total score.	Not all participants completed all of programme. 5/20 lost to follow up	Not reported	4
Nardone et al. (2014) **Italy**	Before/ After (Retrospective)	Age 16-79 years. Child was male.	N=27 *1 patient under 16 (stroke n=14, degen disease n=13)	Cerebellar stroke and degenerative cerebellar disease. Child was 3 yrs post diagnosis of cerebellar ataxia	All ambulatory (+/- aid which was specified)	Intensive rehabilitation input, including mixed training; static balance, dynamic control, gait training, flexibility and strength training.	3 weeks, 90 minutes x 5 a week	Not reported	Postural stability (body sway) Gait parameters, Balance impairment, FIM (motor and cognitive component)	Unable to extract results for 16 year old. Overall reported significant reduction in body sway post intervention in both groups. BBS significantly improved in both groups. Gait parameters and FIM improved more in vascular group.	No loss to follow up reported	Not reported	4
Sabel et al. (2016) **Sweden**	Cross over (Active video gaming and coaching Vs wait list and usual care)	Age 6-17 years. 6 male 7 female.	N=13 (PFT n=3, supratentorial tumour n=10)	Children with brain tumours 1-5 years post diagnosis.	All able to stand	Active video gaming using the Wii in home setting. Virtual training games focus on balance.	10 weeks, 30 minutes x 5 a week	Unsupervised after initial home visit. Virtual coaching by research nurse weekly.	BOT2 Sense wear arm band to record physical activity	Unable to extract results for PFT group. Overall 15% improvement in body coordination score post intervention (4.55 scale points). Stat sig improvement in bilat coordination score. No sig change in balance score	Diary to report compliance, achieved target x5 a week	Not reported	3
Santos et al. (2017) **Brazil**	Before/After	Age 15-70. 20 male, 8 female.	N=28 1 child (15 yrs) with SCA diagnosed 3 years earlier	Participants with SCA.	SARA score 4-28	VR rehabilitation using the Wii balance board. 4 balance games played.	Twenty sessions of 50 minutes twice a week	Not specified	BBS, Dizziness Handicap Inventory (DHI), Short Form Health Survey (SF-36)	Unable to extract results for child with ataxia. Overall significant improvements in BBS and DHI score post intervention. Significant improvements in fall frequency.	Not reported	Not reported	4

Schroeder et al. (2014) **Germany**	Before/ After (2 pre intervention, one post intervention)	Mean age 9.3 years 30 Female, 40 male.	Whole cohort N=83, complete data for N=70 *2 children with ataxia	Children with CP	All GMFCS levels	Robot enhanced treadmill therapy and usual care.	4 weeks, 12 sessions	Supervised by therapist	GMFM 66 dimension D and E	Data for children with ataxia not reported separately. Immediately post intervention mean differences in GMFM for the whole group.	Complete data 70/83. Fidelity reported in terms of mean dose though targeted dose not reported.	Not reported	4
Van Hedel et al. (2016) **Switzerland**	Retrospective before/after	Age 3-19. 26 female, 41 male.	N=67 *6 children with ataxia	Children with CP	GMFCS level II-IV	Robot assisted gait training with the Lokomat complementing a MDT rehab program	Average of 3-5 Lokomat sessions per week plus 4-5 physio sessions per week. As retrospective review no set defined protocol. Average total RAGT sessions was 20	Therapist supervised, (N=57 inpatients)	Functional Ambulation Categories (FAC), WeeFIM, GMFM dimension D and E, 6MWT, 10MWT.	Data for children with ataxia not reported separately. ST: No sig change in FAC on discharge. Significant improvements in WeeFIM transfer and walk items, mobility and total WeeFIM items. Significant improvement in 10MWT. No sig change in GMFM.	Not reported	Not reported	4

Appendix 5 – COSMIN Risk of Bias Checklist (Mokkink et al. 2018b) - Box 10 Responsiveness

10d. Construct approach: (i.e. hypotheses testing: before and after intervention)					
Design requirements	very good	adequate	doubtful	inadequate	NA
11 Was an adequate description provided of the intervention given?	Adequate description of the intervention		Poor description of the intervention	NO description of the intervention	
Statistical methods					
12 Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
Other					
13 Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

10b. Construct approach (i.e. hypotheses testing; comparison with other outcome measurement instruments)					
Design requirements	very good	adequate	doubtful	inadequate	NA
4 Is it clear what the comparator instrument(s) measure(s)?	Constructs measured by the comparator instrument(s) is clear			Constructs measured by the comparator instrument(s) is not clear	
5 Were the measurement properties of the comparator instrument(s) sufficient?	Sufficient measurement properties of the comparator instrument(s) in a population similar to the study population	Sufficient measurement properties of the comparator instrument(s) but not sure if these apply to the study population	Some information on measurement properties of the comparator instrument(s) in any study population	NO information on the measurement properties of the comparator instrument(s) OR evidence of poor quality of comparator instrument(s)	
Statistical methods					
6 Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method were appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
Other					
7 Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

10c. Construct approach: (i.e. hypotheses testing: comparison between subgroups)					
Design requirements	very good	adequate	doubtful	inadequate	NA
8 Was an adequate description provided of important characteristics of the subgroups?	Adequate description of the important characteristics of the subgroups	Adequate description of most of the important characteristics of the subgroups	Poor or no description of the important characteristics of the subgroups		
Statistical methods					
9 Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
Other					
10 Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

Box J. Interpretability

		yes	no	?
1	Was the percentage of missing items given?	☐	☐	
2	Was there a description of how missing items were handled?	☐	☐	
3	Was the sample size included in the analysis adequate?	☐	☐	☐
4	Was the distribution of the (total) scores in the study sample described?	☐	☐	
5	Was the percentage of the respondents who had the lowest possible (total) score described?	☐	☐	
6	Was the percentage of the respondents who had the highest possible (total) score described?	☐	☐	
7	Were scores and change scores (i.e. means and SD) presented for relevant (sub) groups? e.g. for normative groups, subgroups of patients, or the general population	☐	☐	
8	Was the minimal important change (MIC) or the minimal important difference (MID) determined?	☐	☐	
9	Were there any important flaws in the design or methods of the study?	☐	☐	

Appendix 6 – Rater protocol – CARS Study

Comparison of the use of two ataxia rating scales in children with brain tumours (CARS Study) – RATER PROTOCOL

- Introduce self to child and family/carers
- Complete the outcome measures in the pre allocated random order
- Complete each outcome measure in full before moving onto the next outcome measure
- Begin timing at the start of the first item of each measure and stop the stopwatch immediately after the completion of the last item
- Ensure adequate space for assessing prior to commencement of the outcome measures

- When completing the SARA;
    - The child should be barefoot (not included in the timing)
    - Use the instructions at the beginning of each item (language can be adapted for differing age groups)
    - Visual prompts can be used if required
    - The items can be completed in any order
    - Record each score on the SARA sheet

- When completing the BARS;
    - The items can be completed in any order
    - The gait item is completed over a 10m distance (pre marked before the start of the test)
    - Visual prompts can be used if required
    - Record each score on the BARS sheet

- When completing the PEDI;
    - complete the mobility domain of the PEDI
    - items should be scored as 0 (unable) or 1 (capable)
    - capable refers to what child can do without help
    - can score 1 for skills that have mastered earlier and progressed beyond but if have lost skills credit only current capabilities
    - if 2 components of task are listed with an AND statement must be able to do both parts
    - the PEDI can be completed by professional judgment of the therapist or by parent report (or a combination, note items answered by parent)
    - complete the PEDI in conjunction with the manual
    - add the scores at the end (raw score out of 39)

- Record your global clinical impression of ataxia (no, mild, moderate or severe at the end of completing the other outcome measures)
- Any items that are not able to be tested record as NT
- Transfer all scores and times to the data collection sheet
- Give the data collection sheet to the physiotherapy assistant immediately at the end of the assessment
- Do not discuss the results of the outcome measures with the other therapists

Appendix 7 – Initial CARS Study data analysis and results n=44

Data Analysis

Inter rater reliability/Measurement error

The SARA and BARS scores for both raters were illustrated using Bland Altman comparison plots. Correlation coefficients were calculated to assess correlation between the raters for each scale (ICC was not used due to the assessment processes used in the study where two raters out of three assessed the children based on rater availability).

Construct Validity

The correlation of the ataxia scales with the PEDI-m was assessed to quantify the relationship between the ataxia scale score and functional ability (a related construct). It would be expected that a higher ataxia score would lead to a lower functional ability score on the PEDI-m (in keeping with a hypothesis testing approach to construct validity). Specific analysis as follows;

1) Correlation between the SARA and PEDI-m using Spearmans rank correlation coefficient

2) Correlation between the BARS and the PEDI-m using Spearmans rank correlation coefficient

This non parametric test was chosen due to the skewed distribution of the data. In addition, the data was first plotted on a scatter graph to check for a linear relationship.

Please note criterion validity could not be assessed due to there being no existing gold standard outcome measure to use for comparison.

Feasibility/face validity

To establish further information regarding feasibility and practicality of use in the clinical setting the median time to taken to carry out each outcome measure was calculated. Rater feedback was also collected regarding ease of administration and clinician feedback regarding content of the scales.

Correlation between the scales

The correlation between the SARA and the BARS was also assessed to quantify the relationship between the ataxia scales. Although noted the BARS does include an eye movement item it would be expected a higher score on the BARS scale would be associated with a high score on the SARA scale as both report to measure the same construct of ataxia.

Results

Inter-rater Reliability – Original CARS study n=44

The Bland Altman comparison plots (Figure App7.1 and 7.2) illustrated no systematic difference between the two raters on both the SARA and BARS. In both plots only two observations lie outside the limits of agreement, which is within statistical expectation. (If there was an obvious difference between raters then would expect more observations to lie outside the limits of agreement. Also, there is no obvious structure in the differences). The Bland Altman plots can also be seen as a reflection of measurement error.

The correlation coefficients between the two raters were high, 0.94 for the SARA and 0.91 for the BARS (Table App 7.1). There was minimal disagreement between raters; 37 out of 40 (93%) paired SARA total scores and 36 out of 40 (90%) paired BARS total scores were within 2 points of each other (Table App 7.2).

Figure App 7.1 Bland-Altman methods comparison plot - SARA[4]

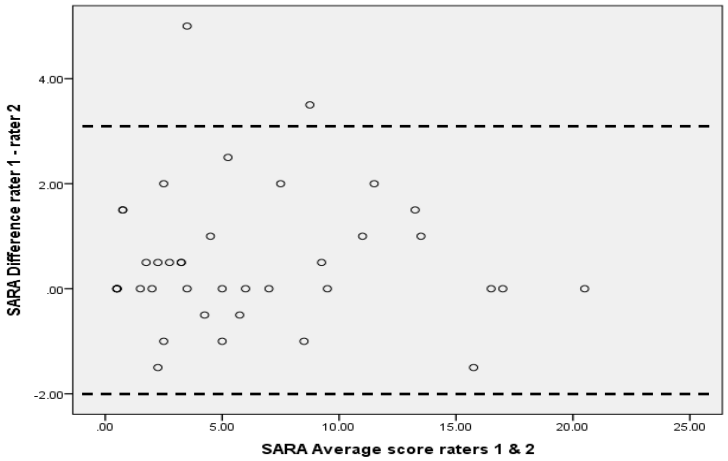


Figure App7.2 Bland-Altman methods comparison plot - BARS[4]

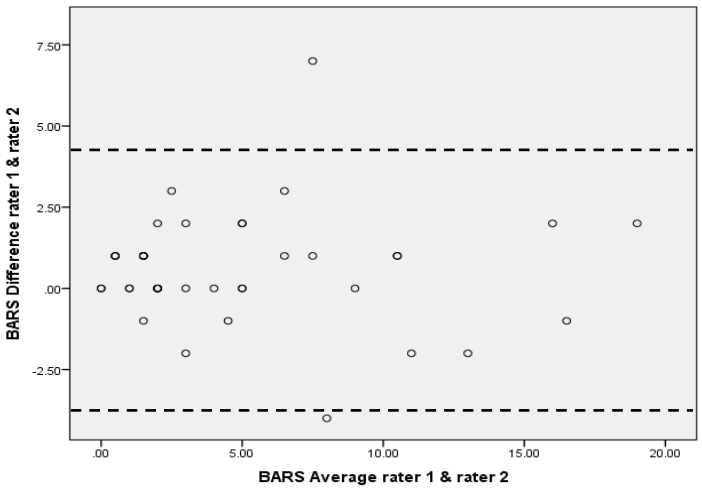


Table App7.1: Correlation

Comparison	Correlation coefficient
SARA rater 1 against SARA rater 2	0.94[3]
BARS rater 1 against BARS rater 2	0.91[3]

Table App7.2: Disagreement

Difference in scores	SARA[5]	Difference in scores	BARS[5]
0	14	0	13
0.5 or 1	15	1	14
1.5 or 2	8	2	9
2.5 or 3	1	3	2
3.5 or 4	1	4	1
4.5 or 5	1	7	1

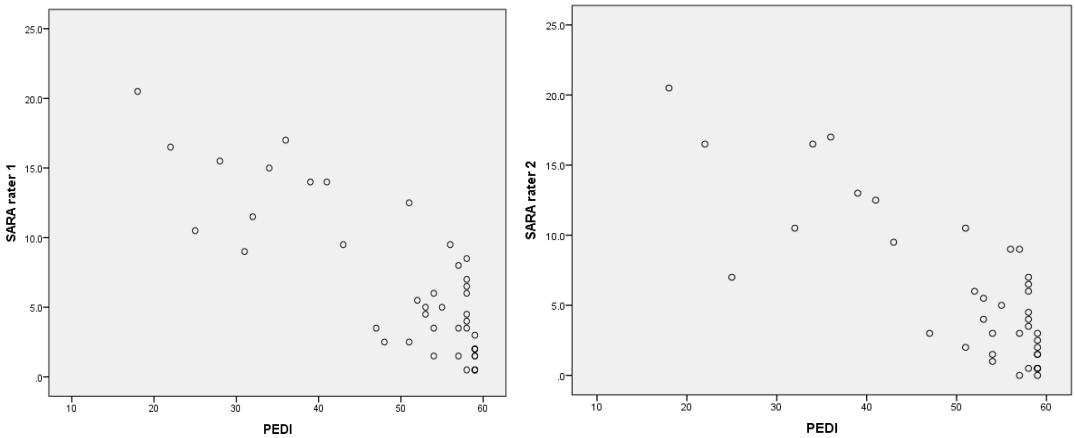
[5] Only 40 observations due to 4 missing values for second rater

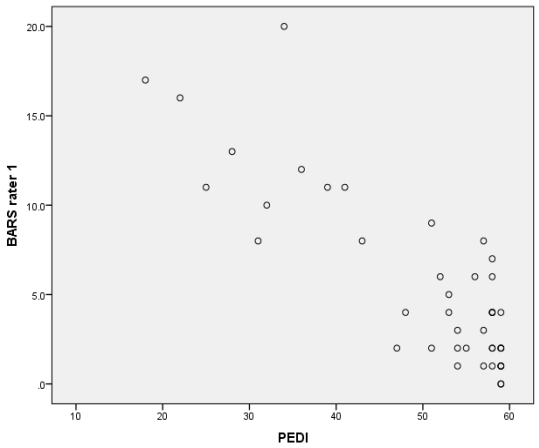
Construct Validity – Original CARS study n=44

The correlation of the SARA and the BARS (for rater 1) against the PEDI-m was determined using the Spearmans's Rank correlation coefficient to quantify the relationship between the ataxia scale score and the functional ability (Figure App 7.3). Non parametric tests were used as the data was not normally distributed.

The SARA demonstrated a strong correlation with the PEDI-m (rater 1, r=-0.77); lower SARA scores were associated with higher PEDI-m scores. The BARS also demonstrated a good association with the PEDI-m (rater 1, r=-0.76) (Table App 7.3).

Figure App 7.3 Scatter plot of participants scores of ataxia scales against their PEDI mobility domain scores





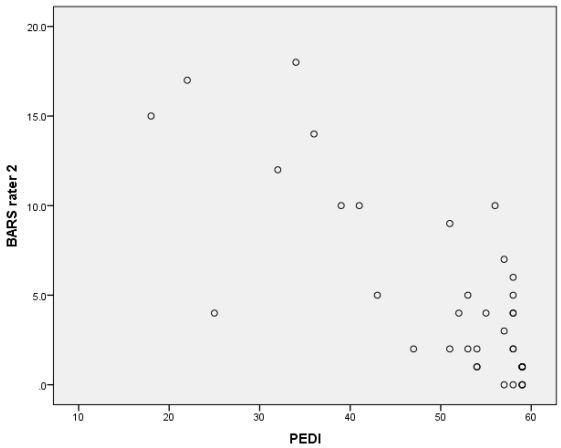


Table App 7.3: Correlation

Comparison	Correlation coefficient
SARA rater 1 against PEDI-m	-0.77[3]
SARA rater 2 against PEDI-m	-0.74[3]
BARS rater 1 against PEDI -m	-0.76[3]
BARS rater 2 against PEDI-m	-0.74[3]

[3]Spearman's rank correlation

Feasibility/Face Validity – Original CARS study n=44

The mean time to complete the SARA was 4.5 minutes (SD 1.49); range 2.0-9.0) and the mean time for the BARS was 2.7 minutes (SD 1.36; range 1.0-8.0). Full details are presented in Table App 7.4.

Table App 7.4: Average time to complete

Instrument	***Average time***	***Standard deviation***	***Range***
SARA[1]	4.49	1.49	(2, 9)
BARS[1]	2.73	1.36	(1, 8)
	Mean difference	*95% Confidence interval*	*Significance*
Difference SARA-BARS	1.76	(1.48, 2.05)	<0.001[2]

[1] n=84

[2] Independent sample T-test

The three raters provided their feedback on the ataxia scales in terms of; ease of administration, ease of interpretation, covering the content that would be expected. A five-point Likert scale was used from strongly disagree to strongly agree for potential answers. The results are presented in Table App 7.5**.**

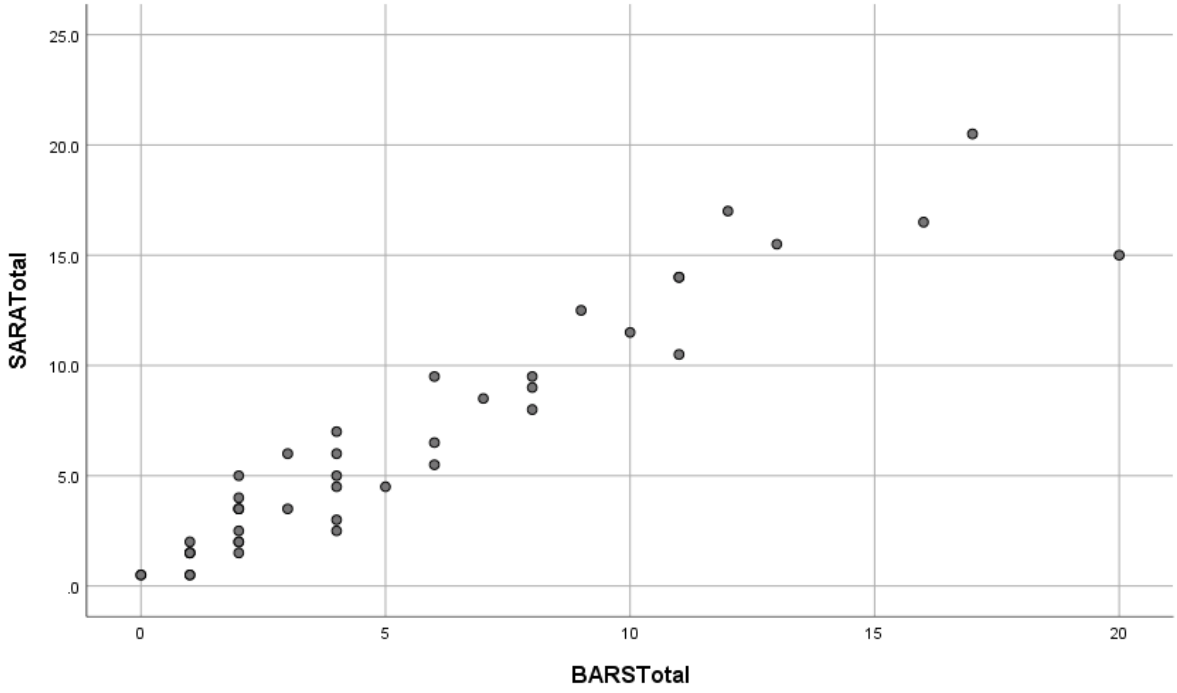
Table App 7.5: Rater Feedback n=3

Question	SARA Scale	BARS Scale
It is easy to administer	1 strongly agree 2 agree	3 agree
It is easy to interpret	3 agree	1 agree 2 disagree
It covers the content I would expect it to	3 strongly agree	3 agree

Correlation between the SARA and BARS scale (n=44)

The correlation of the SARA with the BARS (for rater 1) against was determined using the Spearmans's Rank correlation coefficient to quantify the relationship between the ataxia scales. The SARA demonstrated a strong correlation with the BARS (rater 1, r=0.95); lower SARA scores were associated with lower BARS scores. This is illustrated in the figure below (Figure App 7.4). This would be expected as both scales report to measure the same construct of ataxia.

Figure App7.4 Scatter plot of participants SARA scores against their BARS scores for rater 1



[Please note internal consistency was not analysed as this was done in the initial adult study during development of the tool and was not relevant to the research question]

Appendix 8 – CARS Study Global Impression of Change

Comparison of two ataxia rating scales (CARS Study)

CLINICIAN GLOBAL IMPRESSION OF CHANGE
How has the patient's ataxia changed since their last assessment?

Very much better ☐
Much better ☐
Minimally better ☐
No change ☐
Minimally worse ☐
Much worse ☐
Very much worse

PATIENT/FAMILY/CARER GLOBAL IMPRESSION OF CHANGE
How has your/your child's ataxia/co-ordination changed since their last assessment?

Very much better ☐
Much better ☐
Minimally better ☐
No change ☐
Minimally worse ☐
Much worse ☐
Very much worse ☐

If not done please record (and reason)
_____

Appendix 9 – Additional analysis for CARS extension study

Analysis of scales compared with GCI-change (supporting information for section 5.8.2.1)

The 'stable' and 'acute' cohort (assessments between year 2 and 3) were reviewed to ensure it was appropriate to combine the dataset for further analysis. This information is presented below in Table App 9.1

Table App 9.1 GCI Change scores in stable cohort versus acute cohort at year 2 and 3

	Very much worse	Much worse	Minimally worse	Same	Minimally better	Much better	Very much better
Stable Cohort N=36	0	0	1	12	7	5	0
Acute cohort N=23	0	0	0	19	8	0	0

Missing data n=7

Additional analysis was also completed to examine change in SARA and BARS scores between acute participants (baseline to 3 months, 3 months to 1 year) compared with GCI-change to see if this supports the results analysed in the 'stable' group. This is presented below in Table App 9.2 and 9.3

Change for longitudinal participants between baseline and 1-year (supporting information for section 5.8.2)

Table App 9.2 GCI-Change for longitudinal acute participants between baseline and 3 months

Change	N	SARA change (range)	BARS change (range)
Minimally Worse	0	n/a	n/a
Same	1	-1	0
Minimally Better	8	-12 to +1	-14 to 0
Much better	14	-15 to -1.5	-1 to -9
Missing	7	n/a	n/a

Table App 9.3 GCI-Change for longitudinal acute participants between 3 months and 1 year

Change	N	SARA change (range)	BARS change (range)
Minimally Worse	0	n/a	n/a
Same	3	-1 to 0	-1 to +2
Minimally Better	12	-3 to 0.5	-3 to +3
Much better	9	-3 to 0	-4 to +2
Missing	6	n/a	n/a

Data analysis for longitudinal participants assessed acutely (within the first year post operatively) supports the ability of the SARA and BARS to identify an improvement in ataxia, although again there is overlap between minimally and much better groups indicating a lack of ability to differentiate between these. The SARA change for children assessed between 3 months and 1 year particularly is similar to that of the 'stable cohort' presented in Chapter 8. It is observed there is wider variation in BARS scores for children assessed between 3 months and 1 year than in SARA scores, i.e. an increase in score is noted where this would not be expected for children who were reported to be minimally/much better. On further examination this relates to 2 individual children where BARS score increased despite being reported to be minimally/much better, however, the SARA score did not increase in these cases which does fit with expectations. It would therefore be of value to explore these cases further to understand this better, e.g. to determine if there was any visual deterioration which might account for the changes in score.

Global clinical impression of ataxia as rated by the clinician compared with global clinical impression of change (supporting information for section 5.8.2.1)

Table App 9.4 Illustrates severity classification of ataxia (i.e. no, mild, moderate or severe) compared with global clinical impression of change. E.g., for 19 children who were rated as having no ataxia, 16 were rated the same on reassessment and 3 were rated as minimally better. Whereas there was a wider spread for children who were rated as having moderate ataxia, with 1 child being rated as minimally worse, 1 as the same, 4 as minimally better and 2 as much better. This highlights the consideration that MCID may be influenced by

baseline severity of ataxia. E.g., a child with no or mild ataxia has less room to improve than a child with more significant symptoms.

Table App 9.4 Global Clinical Impression of change (GCI-change) and CGI classification

CGI/Change	Minimally Worse	Same	Minimally Better	Much better
None	0	16	3	0
Mild	0	14	6	3
Moderate	1	1	4	2
Severe	0	0	2	0

Additional data analysis using same method in the PEDI responsiveness paper (Iyer et al. 2003), (supporting information for Section 5.8.2.4)

Table App 9.5 demonstrates analysis for the SARA, BARS and PEDI-m using the same method as the PEDI responsiveness paper, identifying the percentage change in each scale for children reported as minimally better.

Table App 9.5 Percentage change for children reported minimally better

	SARA	BARS	PEDI-m
Same mean (st.dev)	0 (1.13)	-0.067 (1.28)	0.78 (4.70)
Minimum better (st.dev)	-2 (2.28)	-1.8 (1.90)	2.51 (9.92)
Minimum % change	5%	6%	2.5%

Influence of age on ataxia scores (supporting information for section 5.8.2.4)

Additional analysis is presented according to the three age groups that were used by the European Ataxia Group in the normative data (Lawerman et al. 2017a). The tables below demonstrate change in SARA score at each assessment timepoint according to age.

Table App 9.6 Age related changes for SARA scale between baseline and 3 months assessment

Age group	Median change	Maximum change	Minimum change
4 – 7	-4.5	-9.5	0.5
8 – 11	-2.25	-15.0	1.0
12 -16	-3.50	-7.5	-1.5

Table App 9.7 Age related changes for SARA scale between 3 months and 1-year assessment

Age group	Median change	Maximum change	Minimum change
4 – 7	-0.5	-3.0	2.5
8 – 11	-1.0	-4.0	1.5
12 -16	-1.5	-3.0	0.5

Table App 9.8 Age related changes for SARA scale between 1 year and 2-year assessment

Age group	Median change	Maximum change	Minimum change
4 – 7	-0.25	-2.5	1.0
8 – 11	-0.25	-1.5	13.5
12 -16	-1.0	-8.0	2.5

Median age-related values for SARA score in healthy children are presented below in Table App 9.9.

Considering normative data when examining the results of this study, there is a reduction in ataxia in the first 3 months that cannot be explained by maturational changes.

Examining Table App 9.7 the median change for children 8-11 years of age, and 12-16 years of age between 3 months and 1-year post operatively is -1 and -1.5 respectively which again would be in keeping with a reduction in ataxia not explained by maturation.

The 12-16-year-old age group also demonstrate a change that cannot be explained by maturational changes between 1 and 2 years post operatively. It remains difficult to identify recovery from age related maturational changes in younger age groups due to intrinsic variability between rate of maturation in individuals being higher at younger age groups.

Table App 9.9 Age related values of SARA scores in healthy children

Age	4	5	6	7	8	9	10	11	12	13	14	15	16
Lowest value	1.5	0.5	0.5	0	0	0	0	0	0	0	0	0	0
Lower Quartile	3.5	1.5	1.0	0.5	0.5	0.5	0	0	0	0	0	0	0
Median	5.0	2.5	1.5	0.5	1.0	0.5	0.5	0	0	0	0	0	0

Upper quartile	6.5	4.0	2.0	2.0	1.5	1.5	1.0	0.5	0.5	0	0.5	0	0.5
Highest value	7.0	5.0	3.0	3.0	4.0	1.5	2.0	1.5	1.0	0.5	1.0	0.5	1.0

Table of 25%, median and 75% of SARA scores in healthy children per year of age (ref 1)
Calculated from the CACG-EPNS SARA study data, n=156, 12/year (ref 2-3)
For 'real' reference values we would need 120 children per year of age (ref 4)
References;

1. *Lawerman et al. Paediatric motor phenotypes in early onset ataxia, developmental coordination disorder and central hypotonia. Dev Med Child Neurol. 2019 Sep 7*
2. *Brandsma et al. Ataxia rating scales are age dependent in health children. Dev Med Child Neurol. 2014 Jun*
3. *Lawerman et al. Age related reference values for the SARA in children – A European multicentre study. Dev Med Child Neurol. 2017 Oct*
4. *Jones et al. Reference Intervals. Clin Biochem Rev. 2008*

Appendix 10 - E-Survey of current international practice regarding ASsessment and Physiotherapy managEment for Children with ataxia following surgical resection of posterior fossa Tumour (ASPECT Study)

Edge Hill University

Thank you for your interest in undertaking this e-survey. Before you participate, please read the following information to find out more about the e-survey.

Ataxia is the most common motor problem seen in children with posterior fossa tumours and there is a gap in the literature regarding physiotherapy practice for this patient group. The aim of this study is to gain an understanding of the current reported international physiotherapy practice for children with ataxia following management of posterior fossa tumour.

You have been invited to participate in this study because you are a physiotherapist/physical therapist involved in the treatment and assessment of children with posterior fossa tumours. You do not have to take part. If you decide to participate we anticipate it will take about 20 minutes to complete the survey. If you submit your responses to the e-survey this will be deemed to be you consenting for your anonymized data to form part of the study. The anonymized results will be analyzed as part of a NIHR clinical doctoral fellowship and not used for any marketing or promotional purposes. The results may also be published in a scientific journal, used to guide future research and to further knowledge of how to help improve physiotherapy for children with posterior fossa tumours.

If you have any further questions please do not hesitate to contact me.

Helen Hartley
NIHR Clinical Doctoral Fellow
Helen.hartley@alderhey.nhs.uk

(Please note the NIHR Clinical Doctoral Fellowship is a personal training award funded through the National Institute for Health Research for clinicians who wish to obtain a PhD by research whilst continuing to develop their clinical skills)

If you would like to contact the supervisor for the project please find details below.

Prof. Bernie Carter, Professor of Children's Nursing, Faculty of Health and Social Care, Edge Hill University

Bernie.Carter@edgehill.ac.uk

Alternatively, if you wish to discuss any issues regarding this project with an independent point of contact please see details below.

Professor Clare Austin, Associate Director Research and Innovation, Faculty of Health and Social Care, Edge Hill University

austincl@edgehill.ac.uk

Initial Filter Question

Are you a physiotherapist/physical therapist involved in the treatment and assessment of children with posterior fossa tumours

Yes No

(If yes continue to survey, if no directed to page which says thankyou but not eligible to participate**)**

SECTION 1 (Demographics of responder/unit)

1) Location of Unit (e.g. town/city and country)

2) Qualifications (Please tick all that apply)

Physiotherapy/Physical Therapist;

Diploma ☐ Degree (BSc) ☐ MSc ☐ PhD ☐ Other ☐ Please specify

3) Male ☐ Female ☐

4) How many years have you been a qualified physiotherapist?

0-2 years ☐ 3-5 years ☐ 6-9 years ☐ 10 years or over ☐

5) How many years' experience do you have working with children (0-18 years of age) with brain tumours?

0-2 years ☐ 3-5 years ☐ 6-9 years ☐ 10 years or over ☐

6) On average how many children (0-18 years of age) do you treat with posterior fossa tumours per year?

7) What percentage of your caseload is dedicated to managing children with posterior fossa tumours?

8) Have you received any post graduate training in working with children with posterior fossa tumours?

Yes ☐ No ☐

If yes please detail

9) Into which of the following settings do you provide therapy input? (Please tick all that apply)

For the purpose of this survey the following definitions apply;

Inpatients – Child an inpatient in hospital

Outpatients – Child attends as an outpatient to hospital base

Clinic – Specialist clinic in hospital setting e.g. Neuro Oncology/Neurodisability

Community – Child's home/setting local to child but not an education setting

School/Nursery – Education setting

Inpatients ☐ Outpatients ☐ Clinic ☐ Community ☐ School/Nursery ☐

10) Which is your primary setting? (tick one)

Inpatients ☐ Outpatients ☐ Clinic ☐ Community ☐ School/Nursery ☐

11) Do you work as part of a specialist team e.g. Neuro Oncology Rehabilitation Team

Yes ☐ No ☐

If yes please specify; (include team name and members e.g. Physiotherapist, Occupational Therapist, Speech and Language Therapist)

SECTION 2 (Aspects of intervention)

For the purpose of this survey the following definitions apply;

Strengthening training/exercises – Resistance training that involves the body's muscles working or holding against and applied force, with structured increases in training load to increase muscle strength (e.g. using body weight, free/machine weights or resistance bands)

Proximal control exercises – Exercises focusing on proximal stability (e.g. shoulder girdle, trunk, pelvis control)

Task specific training – Practicing a task repeatedly with the aim of acquiring/reacquiring a skill (e.g. repeated sit to stand)

Balance exercises – Exercises with a specific aim to improve balance/postural control that challenge stability and explore stability limits (e.g. exercises for static balance, dynamic balance and proprioception)

Aerobic training – Involves the body's large muscles moving in a rhythmic manner for a sustained period of time without significantly overloading the muscles involved (e.g. walking, running, cycling, swimming)

Endurance training –Also known as cardiovascular training, is a type of aerobic training that includes activities that increase breathing and heart rates but which do not significantly overload the muscles involved

Manual therapy – physical treatment delivered by therapist may include soft tissue mobilization, myofascial release or joint mobilization

Stretching – passive or active stretches with the aim to improve range of movement

Gait re-education – practice/re-education of walking to improve function/walking pattern

Neurodevelopmental Therapy (NDT) – physiotherapy focused on facilitation and normalization of movement patterns

12) Which type of therapy intervention do you use to treat children with posterior fossa tumour/s? (Please tick all that apply)

Strengthening training/exercises ☐ Proximal control activities ☐ Task specific training ☐ Balance exercises ☐ Hydrotherapy ☐ Aerobic Training ☐ Endurance Training ☐ Manual Therapy ☐ Stretching ☐ Gait re-education ☐ Neck range of movement exercises ☐ NDT ☐ Other ☐ Please state

13) Which type of therapy intervention do you use **most often** in children with posterior fossa tumours (Please tick one)

Strengthening training/ exercises ☐ Proximal control activities ☐ Task specific training ☐ Balance exercises ☐ Hydrotherapy ☐ Aerobic Training ☐ Endurance Training ☐ Manual Therapy ☐ Stretching ☐ Gait re-education ☐ Neck range of movement exercises ☐ NDT ☐ Other ☐

14) Which type of therapy intervention do you think is **most effective,** please rank your top 3 interventions; (from the list below)

Strengthening training/ exercises ☐ Proximal control activities ☐ Task specific training ☐ Balance exercises ☐ Hydrotherapy ☐ Aerobic Training ☐ Endurance Training ☐ Manual Therapy ☐ Stretching ☐ Gait re-education ☐ Neck range of movement exercises ☐ NDT ☐ Other ☐ Please state

15) What adjuncts to therapy intervention do you use in children with posterior fossa tumours? (Please tick all that apply)

For the purpose of this survey the following definitions apply;

Virtual Training - refers to the use of computer technologies that provide aninteractive environment that requires limb movement to react to on screen game play (e.g. Wii, X Box, Apps, Specific therapy developed software, Exergames, virtual reality headset/goggles)

FES – Functional Electrical Stimulation – refers to the application of electrical current to the nerves that control muscle during a functional activity

Treadmill training/Body weight support treadmill training (BWSTT) – combines partial body weight support with the use of a harness and treadmill training

Weighted therapy - refers to the use of weighted products to apply pressure to the body e.g. wrist weights to help with upper limb control

Hippotherapy – provision of sensory and motor input via the movements of a horse with programmes designed by individuals with hippotherapy qualifications

Physiotherapy led yoga/pilates – Physiotherapist instructing in yoga/Pilates sessions

Biofeedback –use of auditory/visual biofeedback from an external source (e.g. visually following images whilst performing functional tasks)

Orthotics ☐ Taping ☐ Lycra® Garments☐ Virtual training ☐ Electrical stimulation/FES ☐ Treadmill training/BWSTT☐ Weighted therapy ☐ Walking/mobility aids ☐ Hippotherapy ☐ Physiotherapy led yoga/Pilates ☐ Biofeedback ☐ Other ☐ None ☐

16) Which of these adjuncts do you use **most often**? (Please tick one)

Orthotics ☐ Taping ☐ Lycra® Garments☐ Virtual training ☐ Electrical stimulation/FES ☐ Treadmill training ☐ Weighted therapy ☐ Walking/mobility aids ☐ Hippotherapy ☐ Physiotherapy led yoga/Pilates ☐ Biofeedback ☐ Other ☐ None ☐

17) Which of these adjuncts do you think is most effective? (Please rank your top 3 adjuncts from the list below)

Orthotics ☐ Taping ☐ Lycra® Garments ☐ Virtual training ☐ Electrical stimulation/FES ☐ Treadmill training ☐ Weighted therapy ☐ Walking/mobility aids ☐ Hippotherapy ☐ Physiotherapy led yoga/pilates ☐ Biofeedback ☐ Other ☐ None ☐

18) Do you base your intervention on any guidelines?

Yes ☐ No ☐

If yes please give details;

Local ☐ International ☐

19) Do you base your intervention on any evidence based practice?

Yes ☐ No ☐

If yes please give details

SECTION 3 (Virtual Training)

Virtual Training - refers to the use of computer technologies that provide an interactive environment that requires limb movement to react to on screen game play (e.g. Wii, X Box, Apps, Specific therapy developed software, Exergames, virtual reality headset/goggles)

20) Have you used virtual training (e.g. Wii/X Box Kinect) in your overall practice?

Yes ☐ No ☐

If yes which population have you used this in;

Cerebral Palsy ☐ Developmental Delay ☐ Traumatic Brain Injury ☐ Acquired Brain Injury (excluding posterior fossa tumours) ☐ Posterior fossa tumours☐ Other ☐ Please state

21) If you have used virtual training in children with posterior fossa tumours;

Please list the top 3 things you have found most beneficial with this intervention

i)

ii)

iii)

Please list the top 3 challenges you have identified through using virtual training

i)

ii)

iii)

Have you found solutions to these challenges?

Yes ☐ No ☐

If yes please detail

i)

ii)

iii)

22) Have you recommended to families to continue to use virtual training as part of their home exercise programme?

Yes ☐ No ☐

If yes, did the families report any difficulties with using this?

Please state

Section 4 (Intensity of treatment)

23) Do you typically intensify your rehabilitation for children with posterior fossa tumours at certain time points?

Yes ☐ No ☐

If yes please tick when this most often occurs

Immediately post operatively☐ Following completion of all adjunct treatment such as radiotherapy/chemotherapy ☐ Other ☐ Please state

24) How often do you typically treat these children in the **inpatient setting**?

4-5 times per week ☐ 2-3 times per week ☐ once a week ☐
Fortnightly ☐ Monthly ☐ Other ☐ Please state

25) How often do you typically treat these children in the **outpatient/community or school setting**?

4-5 times per week ☐ 2-3 times per week ☐ once a week ☐ Fortnightly ☐ Monthly ☐ Block of therapy treatment followed by review ☐ Other ☐ Please state

26) What is the average length of a physiotherapy session?

Under 30 minutes ☐ 30-<45 minutes ☐ 45-<60 minutes ☐ Over 60 minutes ☐

27) How long (on average) does therapy intervention continue for children with posterior fossa tumours?

0-3 months ☐ 4-6 months ☐ 7-12 months ☐ 1-2 years ☐ Over 2 years☐

28) How is physiotherapy input primarily delivered?

1:1 by physiotherapist ☐ 1:1 by therapy assistant ☐ group setting ☐ Home exercise programme ☐

Section 5 (Aims /Outcomes and Challenges)

29) What are your typical aims of physiotherapy treatment (tick all that apply)

Improve co-ordination ☐ Improve balance ☐ Improve muscle strength ☐ Improve aerobic fitness ☐ Educate child/family regarding activity ☐ Improve range of movement ☐ Help/assist with return to school ☐ Help with return to sports ☐ Reduce pain ☐

30) What factors do you take into account when goal setting with this group of patients? (Please list the 3 most important factors)

31) Do you use standardized outcome measures in children with posterior fossa tumours?

Yes ☐ No ☐

If yes please state the outcome measures you use most frequently

32) Are there any frequent problems/challenges you encounter when treating children following surgical resection of posterior fossa tumour? *Please consider potential issues from a broad perspective (e.g. availability of staff and services, availability of evidence, mentoring, psychosocial issues, impact of adjuvant treatment such as radiotherapy and chemotherapy)*

33) Please list any common problems you have identified in relation to therapy management with the transition from inpatient to outpatient setting

i)

ii)

34) Please list any common problems you have identified in relation to therapy management with reintegration into the school setting

i)

ii)

35) Please list any common problems you have identified in relation to therapy management with transition to adult services

i)

ii)

36) What are your main reasons for discharging a child who presented with ataxia following surgical resection of posterior fossa tumour?

Please tick the 3 most common from the list below

Childs goals have been met ☐ Plateau in physical function ☐ Return to full time education ☐ Return to sporting activity ☐ Return to pre operative level of function ☐ Lack of funding available for therapy ☐ Limitations of health insurance ☐ Therapy capacity/caseload demands ☐ Other ☐ Please state

Thank you for taking the time to complete this survey

Appendix 11 – FREC approval for e-survey

Edge Hill
University

Helen Hartley

15th May 2017

Dear Helen,

Thank you for submitting your research ethics application '*E-survey of current international practice regarding the ASessment of Physiotherapy management for Children with ataxia following surgical resection of posterior fossa Tumour (ASPECT Study)*' (FOHS 170) to the Faculty of Health & Social Care Research Ethics Committee.

I have pleasure in informing you that the Committee recommended that your study is granted Faculty of Health & Social Care research ethics approval, subject to the following conditions:

1. Ethical approval covers only the original study for which it is sought. If the study is extended, changed, and / or further use of samples or data is needed the Committee Administrator, Daniel Brown, must be contacted for advice as to whether additional ethical approval is required.

2. (NHS studies only) NHS Research governance processes must be adhered to. An application must be made to the HRA for approval for the research to be conducted in the NHS. All NHS R&D departments (in Trusts where data is being collected) will also need to be approached for Trust permission to proceed.

3. If the project requires HRA approval and/or NHS ethical approval, please forward evidence of the approval(s) to Daniel Brown (browdan@edgehill.ac.uk) before commencing the study

4. The Principle Investigator is responsible for ensuring that all data are stored and ultimately disposed of securely in accordance with the Data Protection Act (1998) and as detailed within the approved proposal.

5. The Principle Investigator is responsible for ensuring that an annual monitoring form and an end of study form, where appropriate, is sent to the Committee Administrator (browdan@edgehill.ac.uk). The form will be sent to you at the appropriate time by the Committee Administrator.

6. Ethical approval for this research will expire on 30/09/2017. Any extensions to this date will require additional approval from the committee.

The study documentation that has been reviewed and approved is detailed below:

Yours sincerely

Professor Mary O'Brien

Chair of Faculty of Health & Social Care Research Ethics Committee
Edge Hill University
St Helens Road
Ormskirk
Lancashire
L39 4QP
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Appendix 12 – E-survey paper

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VOL. 2, 2019 ARTICLE 1000020

ORIGINAL REPORT

E-SURVEY OF CURRENT INTERNATIONAL PHYSIOTHERAPY PRACTICE FOR CHILDREN WITH ATAXIA FOLLOWING SURGICAL RESECTION OF POSTERIOR FOSSA TUMOUR

Helen HARTLEY, MSc[1], Bernie CARTER, PhD[2], Lisa BUNN, PhD[3], Barry PIZER, FRCPCH[4], Steven LANE, PhD[5], Ram KUMAR, MRCP[6] and Elizabeth CASSIDY, PhD[7]

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[2]Children's Nursing, Edge Hill University, Ormskirk, UK
[3]School of Health Professions, University of Plymouth, Plymouth, UK
[4]Oncology Department, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
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[7]Department of Physiotherapy, LUNEX International University of Sport, Exercise and Health, Differdange, Luxemburg

Objective: **To determine current international practice regarding physiotherapy input for children with ataxia following surgery for posterior fossa tumour.**
Design: **An e-survey covering the following domains: participant demographics, treatment/intervention, virtual training, intensity/timing of treatment, and aims and outcomes of physiotherapy management.**
Participants: **Physiotherapists involved in the management of children with ataxia following surgical resection of posterior fossa tumour. Participants were contacted via 6 key groups; Paediatric Oncology Physiotherapy Network (POPs), Association of Paediatric Chartered Physiotherapists (APCP), European Paediatric Neurology Society (EPNS), International Society of Paediatric Oncology (SIOP)-Europe Brain Tumour Group, Posterior Fossa Society (PFS), and Pediatric Oncology Special Interest Group (SIG) (American Physical Therapy Association).**
Results: **A total of 96 physiotherapists participated: UK ($n=53$), rest of Europe ($n=23$), USA/Canada ($n=10$), and Australia/NZ ($n=10$). The most common physiotherapy interventions used were balance exercises, gait re-education and proximal control activities. The most frequently used adjuncts to treatment were mobility aids and orthotics. Challenges reported regarding physiotherapy treatment were: reduced availability of physiotherapy input following discharge from the acute setting, lack of evidence, impact of adjuvant oncology treatment, and psychosocial impact.**

LAY ABSTRACT

The aim of this study was to determine how physiotherapists in different countries currently treat children with balance/coordination problems following surgery for a brain tumour. An e-survey, with questions on type of physiotherapy treatment, intensity and timing of treatment, and aims and outcomes of physiotherapy management, was sent to special interest groups, which included physiotherapists with expertise in this area. A total of 96 physiotherapists participated in the survey. The most common physiotherapy treatments used were balance exercises and gait re-education. Mobility aids and orthotics (e.g. splints) were also commonly used. Physiotherapists reported challenges to treatment, including lack of availability of physiotherapy following discharge from hospital, lack of evidence to guide treatment, and impact of oncology treatment (e.g. chemotherapy/radiotherapy) on the child's rehabilitation. In conclusion, there is little evidence in this area. The results of this survey provide an initial basis to understand the challenges of treatment and to plan future research.

Conclusion: **This e-survey provides an initial scoping review of international physiotherapy practice in this area. It establishes a foundation for future research on improving rehabilitation of ataxia in this population.**

Key words: paediatric; brain neoplasm; ataxia; rehabilitation; cerebellum.

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Brain tumours are the most common group of solid tumours in childhood, accounting for almost one-quarter of all paediatric neoplasms worldwide (1). Approximately 50% of all childhood brain tumours are located in the posterior fossa region (2). Management of posterior fossa tumours (PFTs) typically involves surgical resection, solely or in combination with adjuvant treatment, such as radiotherapy or chemotherapy.

Children with PFT have a distinctive set of issues, including potential for change pre-/post-operatively, rapid onset of ataxia, hydrocephalus and increased intra-cranial pressure, in addition to potential problems from subsequent oncological management, such as radiotherapy. Of these issues, ataxia is the predominant motor problem in children with PFT (3, 4). Ataxia can describe a related number of impairments, including upper-limb control, balance, gait difficulties, oculomotor dysfunction, and speech problems (5). Wilne et al. (6) presented a systematic review and meta-analysis with pooled data from 5 studies of children with PFT (n=476), reporting that 60% of children demonstrated ataxia pre-operatively, indicating the prevalence of ataxia in this population group.

In addition, there is increasing understanding of the long-term impact on mobility in this population group, with up to 70% of children noted to have balance problems following completion of neurosurgical/oncology treatment (3, 7). Following surgical management of PFTs, children are typically referred for rehabilitation, including physiotherapy, yet there is little evidence to guide physiotherapists on how best to assess and treat this population. Balance and coordination problems can be a significant challenge following initial treatment, as these can affect activities of daily living, return to school, and participation with peers (3, 8).

Despite the lack of evidence to guide best practice, it is recognized that physiotherapy is integral to the treatment of children with neurological deficits following management of a brain tumour (9), yet, to date, the practice of physiotherapists in managing children with PFT has not been reported. Understanding current practice could help with development of clinical guidelines and assist with the planning of clinical trials in this population. In order to gain increased knowledge of physiotherapy treatment for children with PFT across different countries, an e-survey was developed to scope current practice.

This is the first study to investigate the current practice of physiotherapists in this population group. The aim of the study was to determine current international practice regarding physiotherapy input for children with ataxia following surgical resection of PFT.

METHODS

Study design

A cross-sectional study design was used, with data collected via an online survey (e-survey).

Participants

The target population in this study was physiotherapists who were involved in the assessment and treatment of children with ataxia following surgical resection of PFT. The survey (in English) was disseminated via the Paediatric Physiotherapy Network groups of Paediatric Neurosciences Physiotherapists and Paediatric Oncology Physiotherapists (both UK-based groups), the Association of Paediatric Chartered Physiotherapists (APCP), International Society of Paediatric Oncology European Brain Tumour group (SIOP), Children's Oncology Group (COG) (international membership), Paediatric Physical Therapist Special Interest Group (USA), Posterior Fossa Society (international multidisciplinary special interest group), and European Paediatric Neurology Society (EPNS). "Snowballing" was encouraged, through an automatic request as part of the e-survey to forward the link to therapy colleagues with an interest in this area.

The study was approved by Edge Hill University FOHSC Research Ethics Committee (FOHSC 170).

Instrument

A literature search identified no previous surveys on this topic that could be used for this study. An e-survey (SurveyMonkey®) was therefore designed by the research team (who have clinical expertise in this field and a background in survey development) to ensure that the specific aim of this study was met. The e-survey had 5 domains (**Table I**), with a mixture of open and closed questions. The survey began with an initial filter question checking that respondents were physiotherapists working with children with PFTs. Selecting "no" to the filter question directed potential re-

Table I. Structure of e-survey

Section	Title	Examples of content	Question type
Section One	Demographics	Location of workplace, qualification, years post-qualification, number of children with brain tumours treated per year	8 multiple choice tick-box questions 3 short-answer questions
Section Two	Treatment and Intervention	Type of therapy intervention used most frequently and adjuncts to therapy	7 multiple choice tick-box questions
Section Three	Virtual Training	Benefits/challenges of using virtual training in this population group	1 multiple choice tick-box question 1 multiple choice with option for short answer 3 open questions
Section Four	Intensity and Timing	Length of physiotherapy sessions, and dosage	6 multiple choice tick-box questions
Section Five	Aims and Outcomes	Common aims of therapy and outcome measures used	3 multiple choice tick-box questions 5 open-ended questions

spondents to an automatic response that ended their participation.

The e-survey included a section on virtual training (defined as the use of computer technologies that provide an interactive environment requiring limb movement to react to on-screen game-play (10)), reflecting the recent trend towards the use of technology in paediatric neuro-rehabilitation (11, 12). This section was also planned to inform development of a future RCT examining virtual training intervention in children with ataxia following surgical resection of PFTs.

Prior to disseminating the e-survey it was piloted in order to optimize face and content validity and reliability (13). Four clinicians were purposefully selected to ensure that there were 2 contacts from the UK (an acute hospital-based therapist and a community-based therapist), a representative from Europe (speaking English as a second language) and a representative from the USA. Minor changes were made to the questionnaire as a result of the pilot feedback.

Procedure

The e-survey was disseminated via gatekeepers for each of the identified network groups, with permission from each group received to circulate the e-survey to its members. This enabled the gatekeepers to email their members with a link to the e-survey. A short introductory page of the e-survey provided the participants with sufficient information to enable them to reach an informed decision as to whether to participate. The return of the survey was deemed to be the respondent's consent to participate. The respondents were given 2 weeks to respond, then a reminder was sent electronically. All due care and attention was paid to the management of the data, in line with guidance from local policies and the General Data Protection Regulation (GDPR 2018). The respondents' responses were anonymous.

Data analysis

Using SurveyMonkey®, the data were exported into a Microsoft Excel spreadsheet for further analysis. Descriptive statistics were used to report the closed questions. The qualitative analysis was informed by a deductive approach situated in an essentialist framework (reporting the respondents' perceptions and experiences assuming a straightforward relationship between the written responses and the perceptions) (14). All data from selected open questions were transferred from Microsoft Excel into NVivo to allow the data to be read and re-read and initial codes generated. Codes were sorted and organized into groups, and where there was evidence of recurring responses initial themes were developed and subsequently refined.

RESULTS

A total of 120 out of 140 respondents who accessed the survey answered yes to the initial filter question and proceeded to enter the e-survey. It is not possible to report a response rate, since it is not known how many physiotherapists the e-survey reached, due to the method of disseminating the e-survey and subsequent snowballing.

Initial questions were answered by 96 respondents, with some of the later open-ended questions answered by fewer respondents (mean 60 respondents); however, some of these questions were applicable only to certain physiotherapist groups, e.g. if they had used virtual training. Where abbreviations were used by respondents in quotations presented in the paper, these have been written in full for the sake of clarity. Throughout the results section percentage responses are presented, calculated from the number of respondents who answered each individual question.

Table II. Respondent demographics ($n = 96$)

Demographics	Respondents, *n* (%)
Sex	
Male	6 (6)
Female	90 (94)
Qualification (more than 1 option possible)	
Diploma	6 (6)
Degree	72 (75)
MSc	14 (15)
PhD	7 (7)
Location	
UK	53 (56)
Rest of Europe	23 (24)
USA/Canada	10 (10)
Australia/New Zealand	10 (10)

Demographics

Overall, 12 countries were represented, with more than 50 responses from physiotherapists across the UK, 23 from the rest of Europe (including Belgium, Germany, France, Italy, Lithuania, the Netherlands and the Republic of Ireland), 10 from the USA/Canada, and 10 from Australia/New Zealand. Further details are shown in **Table II**.

Fifty-nine percent ($n=56$) of respondents had more than 5 years' experience of working with children with brain tumours. The median number of children with PFT treated per year was 10. Where respondents indicated that they had completed further training, the most common type of training was a short course in either ataxia or oncology.

The primary work setting of the respondents was an inpatient setting (72%, $n=66$), with 66% ($n=61$) of physiotherapists reporting that they worked within a specialist team for neuro-oncology (**Table III**).

Table III. Participant experience/workplace setting ($n = 96$)

Characteristics	Respondents, *n* (%)
Length of experience working with children with brain tumours	
0–2 years	13 (13)
3–5 years	27 (28)
6–9 years	17 (18)
>10 years	39 (41)
Postgraduate training in working with children with posterior fossa tumours	
Yes	22 (23)
No	74 (77)
Primary work setting	
Inpatient	66 (72)
Outpatient	8 (9)
Clinic	4 (4)
Community	11 (12)
School	3 (3)
Work within specialist team for neuro-oncology	
Yes	61 (66)
No	31 (34)

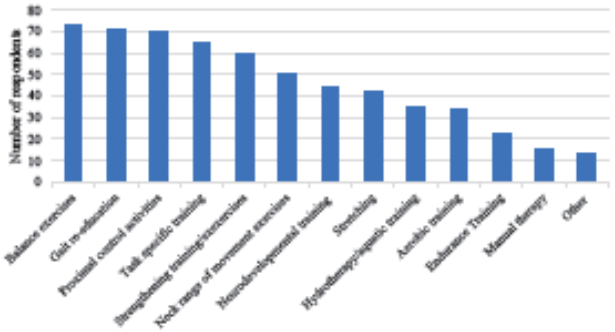

Fig. 1. Types of therapy interventions used.

Therapy intervention

Respondents selected, from a predetermined list, the types of therapy interventions they used in this population group. This question allowed the physiotherapists to indicate all possible interventions they might use, selecting more than 1 possible answer. The results indicate that physiotherapists use a range of interventions, with balance exercises (n=73, 97%), gait re-education (n=71, 95%) and proximal control exercises (n=70, 93%) utilized by the highest number of respondents, as illustrated in **Fig. 1**. Additional types of treatment reported by the respondents in the "other" category included gym ball (n=3, 4%), coordination exercises (n=2, 3%), hippotherapy (n=2, 3%), rebound therapy (n=1, 1%), robotics (n=1, 1%), vocational (n=1, 1%), vojta (involves the therapeutic use of reflex locomotion; www.vojta.com) (n=1, 1%), and approximation exercise (n=1, 1%).

When asked which type of intervention they used most often, 3 intervention types were commonly reported; balance exercises (n=21, 28%), task-specific training (n=17, 23%) and proximal control activities (n=16, 21%). These 3 intervention types were also the most frequently ranked in the therapists "top 3" most effective types of treatment.

Respondents then selected, from a predetermined list of "adjuncts to therapy", which types they used in this population (multiple responses were possible). The results indicate that physiotherapists use a range of adjuncts, with orthotics (n=61, 82%), walking/mobility aids (n=60, 81%) and taping (n=32, 43%) used most frequently (**Fig. 2**). Other adjuncts suggested by the respondents included gym ball activities. Orthotics (n=23, 31%) and walking/mobility aids (n=23, 31%) were the 2 adjuncts used most often by the therapists, and were also the top 2 adjuncts rated as most effective by the physiotherapists. Treadmill training was ranked as the third most effective adjunct to therapy.

Virtual training

Fifty-seven percent of respondents (n=44) reported that they had used virtual training in their practice. The

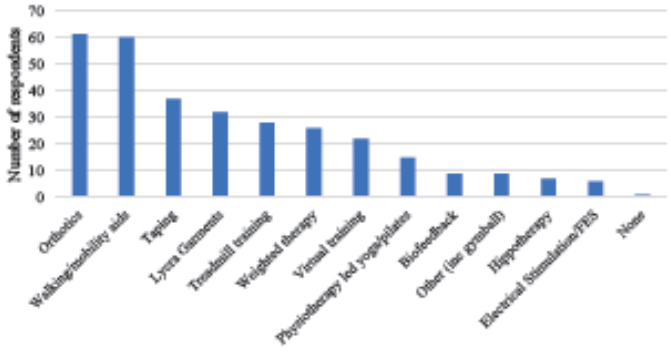

Fig. 2. Types of adjunct to therapy used.

physiotherapists indicated that they had used virtual training most commonly in children with PFTs (n=32, 73%), acquired brain injury (n=28, 64%), and traumatic brain injury (n=27, 61%).

Respondents gave details regarding their top 3 benefits and challenges to using virtual training in their practice, and these answers were thematically analysed. Benefits to using virtual training fell into 3 broad categories; engagement/compliance, physical benefits, and resource/equipment benefits. Engagement/compliance was the most frequently reported benefit, with therapists repeatedly reporting that virtual training was "fun and engaging", and "games are fun". Physiotherapists thought that this method of therapy was "patient friendly" and offered a way to achieve "good compliance" whilst being motivational. Therapists noted the potential physical benefits from using virtual training, which included the ability to work on specific problems, such as upper-limb co-ordination and balance. Resource/equipment factors were also reported as a positive aspect, with 2 respondents noting the potential for the technology to "track progress" and that the technology is easily available, with "no additional equipment required", as children have "access to it at home".

Challenges to using virtual training were also grouped into similar domains; engagement, physical, and equipment/resources. Therapists were concerned that children might become frustrated if they could not play a game that they had been able to play before they had become ill. One therapist highlighted that virtual training might be "demotivating if difficult". Physical barriers/challenges were noted, with therapists raising concerns that, if children had visual difficulties or significant mobility problems, this might limit their potential to use this intervention, with one respondent noting that it could be "difficult if child can't stand". The most frequent response with regard to challenges to virtual training focused on equipment/resource issues. The responses centred on 2 areas; access to the resource or technical difficulties to using it in this specific population. A therapist reported that it was "not timely to set up" and another therapist reported that "it wasn't sensitive enough to use".

Intensity and timing of treatment

The most common frequency of treatment in the inpatient setting was 4–5 times per week (n=31, 42%). Treatment was typically less intense in the outpatient/community setting, although there was a wide range of responses for this setting, ranging from monthly to up to 4–5 times a week. Physiotherapists also reported that they often intensified treatment at specific time-points, although the reasons for this varied, e.g. immediately post-operatively or post-chemotherapy/radiotherapy. The majority of input was delivered on a 1:1 basis by a physiotherapist, with 89% (n=64) of physiotherapists reporting that sessions lasted 30–60 min. Respondents were also asked how long (on average) their therapy intervention continued for children with PFTs. There was variation in responses, with a relatively even spread of answers; from less than 3 months to more than 2 years, which reflected the differing needs of this population group.

Aims and outcomes

Physiotherapists reported common aims for physiotherapy treatment, including improving coordination, balance, muscle strength and providing education to the child/family regarding activity (**Fig. 3**). Other aims identified by the respondents included reducing fatigue and improving participation according to the child's specific goals. Physiotherapists also indicated that they considered several factors when goal-setting for children, typically involving functional and participation targets. These included child-specific factors (e.g. age, pain levels, fatigue) and disease-related factors (e.g. limitations of disease and treatment).

Seventy-five percent (n=52) of physiotherapists (from a total of 69 who responded to this question) reported that they used standardized outcome measures to assess

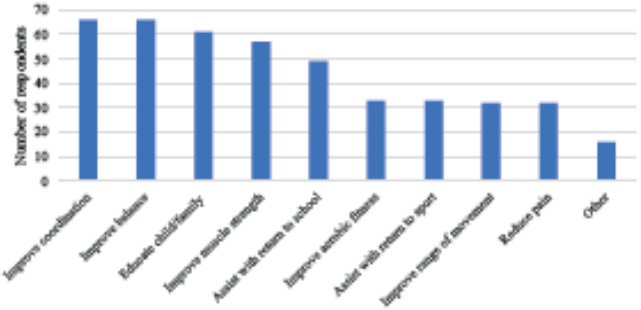

Fig. 3. Aims of physiotherapy treatment.

children with PFTs. The most commonly used outcome measure was the Scale for the Assessment and Rating of Ataxia (SARA) (n=28), followed by the Berg/Paediatric Balance Scale (n=11) and the Gross Motor Function Measure (n=8).

Sixty-nine respondents reported frequent problems/challenges that they encountered when treating children following surgical resection of PFT. Three main themes were identified, each with 2 subthemes (**Fig. 4**). Condition-specific factors included direct medical problems (e.g. the impact of the tumour itself or cerebellar mutism syndrome) or treatment-related issues (e.g. the impact of chemotherapy and radiotherapy, which may include nausea, fatigue or chemotherapy-induced peripheral neuropathy). A number of respondents (n=9) also commented that fatigue can be exacerbated by the child having to travel to another site for radiotherapy; one physiotherapist commented "during radiotherapy patients have to travel, difficulty planning rehabilitation" and another noted that "children transfer to a different hospital for chemo/radio so disjointed service".

Physiotherapists also repeatedly reported challenges to rehabilitation in terms of child and family factors, both from an emotional/psychosocial perspective and expectations/engagement (child and parents). Emotional and psychosocial factors arising from the impact of the illness on the child were reported as challenges by the respondents, such as the "loss of friendship groups and social life". Another physiotherapist noted that "psychosocial issues around functional loss had a huge impact on participation". However, even if the respondents are aware of the potential psychosocial factors and emotional stresses, they reported that it can still be difficult to manage the child's and family's expectations of rehabilitation. The challenge of engaging families in the early stages post-operatively, when the child may be viewed as acutely unwell, was emphasized by therapists, as typified by this response "initially post-op barriers are generally related to family and their views on surgery – families very overprotective with the patients – tend to be slow to get up and move". In addition, following the acute neurosurgical phase there is then the challenge of continuing to integrate rehabilitation during the child's oncology treatment, when, again, they might be unwell. One respondent noted the challenge of "parental coping and mental space to think about rehab versus oncology treatment". This view was supported by another respondent, who noted the "priority of chemotherapy/radiation versus physical therapy". Respondents reported that parents commonly regarded rehabilitation as a low priority until after oncological treatment had finished, as "sometimes the parents don't want the therapists to work with their kids if they are hurting." Engagement directly with the child was also seen as important to maximize therapy sessions, although this challenge was not reported as frequently as the challenge of working with the families. Therapists noted that some children had difficulty engaging with older staff, as they were "too much like mum, just nagging", highlighting the importance of rapport-building between the child and the therapist.

Fig. 4. Problems/challenges encountered when treating children following surgical management of a posterior fossa tumour.

The challenge highlighted most frequently by the therapists related to service delivery of therapy input. This is presented in 2 areas; resource factors and lack of evidence. In terms of resource deficits, the area highlighted was physiotherapy staffing levels, with respondents commenting that "staffing (problem), as often need intensive physiotherapy post-surgery and discharged home". This seemed to be particularly influenced by a perception of pressure to discharge children home quickly, for example, "caseload on a neurosurgical ward – time until discharge to home", alongside problems with subsequent community/local physiotherapy input on discharge home. One respondent described the challenge as being "district general hospital only with limited therapy; community has variable expertise and staffing". In addition to staffing requirements, challenges related to space and equipment were also reported, including "limited space and equipment" and "no dedicated rehab team/ward". In addition to resource issues, the other area that respondents felt directly impacted on physiotherapy input is the lack of evidence for therapy input in this area. This was detailed repeatedly by therapists, who noted the "lack of research" and "limited evidence, especially clinical guidelines".

The final question of the e-survey asked therapists to document their main reasons for discharging a child from their care. The most common answers were if the child's goals had been met (n=50, 71%) or if there was a plateau in physical function (n=43, 61%).

DISCUSSION

This study provides a unique contribution to the understanding of current international practice for children with ataxia following surgical resection of PFTs, and presents new data that have not previously been reported. The lack of evidence to guide physiotherapy practice in this area presents a challenge for therapists integrated in a culture of evidenced-based practice. This study provides an insight to current practice, and a foundation on which to base further exploration of this subject.

Over 90 therapists, from 12 countries, completed the e-survey; although the largest cohort was from the UK, there was good representation internationally, particularly across Europe.

The majority of respondents had been qualified for more than 10 years, suggesting a broad range of experience to draw on when answering questions. However, these experienced therapists also reported looking for, but failing to find, postgraduate training opportunities in this field, indicating that therapists may lack opportunities to develop specialist knowledge. Despite the lack of training opportunities, the UK National Institute for Health and Care Excellence (NICE) neuro-oncology guidelines (9) recommend that clinicians involved in this specialist area should have access to training.

Team working

Two thirds of the therapists reported they worked as part of a specialist Neuro-Oncology Rehabilitation Team. Team working is recognized as important in rehabilitation to enable a cohesive approach with children who have many professionals involved in their care (15), and multidisciplinary team working is reported as best practice in the rehabilitation of adults with brain tumours (16). Team working may be particularly important in children with PFT who have multiple transition points in their care, e.g. from neurosurgery to oncology, into community management, and ultimately into late effects follow-up; thus, communication between professionals is essential (17). The presence of such specialist teams provides the basis of expertise, which could help in the formulation of national clinical guidelines, e.g. as seen recently in the development of the UK Stroke in Childhood Clinical Guidelines (18), although clearly developing evidence-based clinical guidelines would be challenging in view of the lack of evidence in this area.

Therapy interventions

Balance exercises, gait re-education and proximal control exercises were the most commonly used interventions reported by respondents. Balance exercises are regularly used in neurorehabilitation, and there is some evidence of effect for adults with ataxia (5, 19), although a lack of evidence in children with PFTs is noted. The use of proximal control was also widely supported, especially in the UK, and although commonly used as a treatment for ataxia, research evidence to support its efficacy is lacking.

Adjuncts to treatment reflected consistent practice across different countries/level of experience, with orthotics and mobility aids reported to be the most commonly used and deemed the most effective by therapists. This is despite there being no specific evidence published on the effectiveness of mobility aids/orthotics in children with PFTs. Further exploration of the type of orthotics used and the aim of this intervention adjunct may be useful in future research to understand the high frequency of their use.

Virtual training

A number of therapists had used virtual training in some format in their practice, most commonly with children with PFTs. The results are also in keeping with recent trials, which demonstrated a trend towards effectiveness when utilizing technology for therapy management of children with ataxia (11, 20, 21). Therapists identified a number of benefits to using virtual training, both in terms of engagement for the children, which was repeatedly mentioned (and is reported in the literature (22)), and potential clinical gains, such as working on co-ordination. The potential impact on co-ordination is supported by a study in children with Down syndrome (23). However, most studies have focused on balance (11, 24, 25), which did not feature significantly in the therapists' views about the potential benefits of virtual training. Challenges to using virtual training included access to equipment/training requirements, and gaming systems that are not sensitive enough to adapt to specific children's difficulties. Similar benefits and challenges were reported in Levac's (26, 27) exploration of clinician's experiences of virtual reality working with children with acquired brain injury. Therapists were not directly asked which types of virtual training they had utilized, e.g. off-the-shelf or bespoke gaming options, further analysis of which type of virtual training therapists preferred may also be of value in the future.

Intensity of intervention

Commonly, intense in-patient treatment was offered, with intensity reducing following discharge/transition to community settings. There is no specific evidence to support this decision, although workforce structure may be influential. However, there is evidence on the benefit of intense in-patient rehabilitation in the adult brain tumour population, with reports of significant functional gains in the acute rehabilitation process, with the most gain found during the initial inpatient stay (16, 28). Therapists reported that they commonly intensified therapy treatment at certain time-points, with the immediate post-operative period being the most highly intensive treatment phase, which is reflected by increased input in the inpatient setting. However, they also identified a strong trend of individualizing intensity of therapy input, taking a number of factors into account, such as adjuvant treatment, fatigue and availability of ongoing community services. An individualized approach is recommended in paediatric neuro-rehabilitation for other conditions, e.g. in childhood stroke (18).

Aims/individualized approach

An individualized approach was noted in terms of goal-setting, with therapists being aware of condition-specific factors. Although there is no specific literature to support this in the PFT population, the use of individualized goal-

setting is evident in the wider literature on paediatric rehabilitation and, in particular, for children with cerebral palsy, where there is a larger evidence-base (29, 30). The aims of therapy intervention covered the whole International Classification of Functioning Disability and Health (ICF), from those focusing on impairment (e.g. improving balance) to influencing activity (improving fitness) and also considering participation (e.g. assisting with return to sport). Environmental and family factors were also considered in the individualized goal-setting. Three-quarters of therapists reported that they used standardized outcome measures, again highlighting areas of good practice. The SARA (31) was the most commonly used outcome measure, which is encouraging, as its inter-rater reliability and construct validity have been demonstrated in this population group (32). However, the SARA is predominantly an impairment-based outcome measure and activity-based outcome measures, e.g. the PEDI, were less widely used.

Challenges to therapy

This is the first time that physiotherapists' views across different countries have been explored identifying specific challenges to rehabilitation. Three themes emerged; condition-specific factors, child and family factors, and physiotherapy delivery factors. Therapists frequently reported challenges related to engagement/expectations of parents, particularly balancing rehabilitation post-surgery or when the child might be unwell during radiotherapy/chemotherapy, which is unique to this population group. Jones (33) described the emotional reactions the child and their family may experience during the initial period post-diagnosis, reporting shock, confusion and uncertainty about prognosis, treatment and outcomes. Feelings of helplessness, loss of control and frustration due to lack of information can also impact families' acceptance of multidisciplinary therapy input (34), and there is no literature to guide practitioners regarding parental expectations of rehabilitation in children with PFTs.

Study limitations

The e-survey tool was piloted, but not formally validated, prior to use, which means that the survey results must be interpreted with some caution. Despite being aware that many people in the target networks were fluent in English, a known limitation is that the survey was only available in English. In addition, snowballing via the special interest groups means that it is not possible to calculate the response rate.

Targeting special interest groups might raise a potential bias, as members of an interest group are potentially more likely to be following best practice, which could be less representative of the whole professional group. However, in order to gain views from therapists who were experienced in the field this was considered the most appropriate source for the sample population. IP addresses were not captured, in order to anonymize the survey and encourage open responses. However, a limitation of this is that, if network connectivity is lost, the responses stop under this IP log-in, and if the respondent logs in again they are counted as a new respondent. The completion rate for the survey (of all surveys started) was 41%, this was influenced by the fact that some questions were not applicable for all therapists to answer; for example, if they had not worked in a particular setting. However, it was noted that there was a slight tail off in responses towards the end of the survey, which could reflect response fatigue due to the length of the survey. A shorter survey with fewer open questions may have achieved a higher completion rate.

Conclusion

This e-survey demonstrates the wide range of intervention types used by therapists. Common adjuncts to treatment included orthotics and walking aids. Broad consensus was noted in terms of treatment intensity in the in-patient setting. Good areas of practice were demonstrated, including multi-disciplinary team rehabilitation and use of individualized treatment planning and standardized outcome measures. This e-survey also makes an important contribution to understanding the challenges involved in rehabilitation in this population group, whilst establishing the foundation for future research into ataxia rehabilitation interventions.

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Appendix 13 – Use of virtual training in paediatric neuro-rehabilitation

Eleven systematic reviews published between 2009 and 2017 reviewed the effectiveness of VRT on a range of motor and functional outcomes in children with neurological pathology, developmental delay or other movement impairment (summarised in Table App 13.1). Most review authors suggested that the overall quality of the studies was low to moderate (predominantly Oxford Centre for Evidence-Based Medicine (OCEBM) level 2B to 5). The review by Hickman et al. (2017) judged 14 RCTs and two single subject design studies to be level 1; however, some of these studies were considered in the other reviews and determined to be a lower OCEBM level by different authors. Excluding duplications, 85 intervention studies were included in the reviews, indicating a relatively large body of research on VRT in paediatrics. In total, 1391 children and young people aged 4-20 years participated in these studies (including control participants) with the majority being children diagnosed with cerebral palsy. VRT dosage varied significantly between the reported studies, with length of sessions ranging from 3 minutes to 120 minutes (median 30 minutes), frequency ranging from 6 times a day to once a week (median 3 times a week), length of intervention ranging from one session to 24 weeks (median 6 weeks). These dosage variations make any judgements regarding intensity of treatment for practice and research very difficult. Improvements were observed in balance, range of movement, strength and coordination (all body structure and function domains). Therapy treatment 'dosage' is discussed further in Chapter 8 in relation to planning the intervention protocol. Effects on participation were less well reported.

Table App 13.1 Summary of systematic reviews on VRT in children 2009-2017

Author	Aim	Number of Studies	Conclusion(s) (of authors)
Bonnechere et al. (2014)	Effectiveness of VRT in rehabilitation in children with CP	31	No clear conclusion due to different intervention protocols and variation in outcome measures. Improvements in body structure and function impairments reported in individual studies.
Chen et al. (2014)	Effectiveness of VRT on upper limb function in children with CP	14 (18 overall but 14 in meta-analysis)	VRT seemed to be a viable tool to improve upper extremity function in children with CP but suggested more rigorous research needed to confirm this due to limitations in the studies.
Dewar et al. (2015)	Efficacy and effectiveness of exercise interventions to improve postural control in children with CP	3 (3 included on VRT, others on alternative interventions reported)	Only weak evidence to support the use of VRT to improve postural control in children with CP (level II/III)
Fehlings et al. (2013)	Effectiveness of VRT to improve motor performance in individuals with cerebral palsy	24	Overall probable (level B) evidence for VRT interventions to improve lower extremity motor control or function. However, there was inadequate evidence of VRT improving upper limb motor control or function or CVS fitness. Strongest level of evidence exists for the use of VRT to improve gross motor outcomes.
Galvin et al. (2011)	Effectiveness of VRT to improve upper limb function in children with neurological impairment	5	Reported evidence for the use of VRT to improve hand and arm skills is at an emerging stage. Small sample sizes and inconsistencies in outcome measurement limited the ability to generalize findings.
Hickman et al. (2017)	Effectiveness of use of active video gaming (AVG) to improve motor function in children with movement disorders including cerebral palsy, developmental coordination disorder, and Down syndrome.	20	Overall VRT is feasible to use in children with neuromotor problems and there is support to improve motor function, but there is not enough evidence to support the use of VRT as a stand-alone intervention. Suggested the need for further studies to examine the effects of VRT in paediatrics as an adjunct to physiotherapy including the use at home would be useful in the future.
LeBlanc et al. (2013)	Explanation of the relationship between VRT and 9 health and behavioural indicators in paediatrics	9 (for children with neuromotor disorders)	Reported controlled studies show that VRT acutely increase light- to moderate-intensity physical activity; however, the findings about if or how VRT lead to increases in habitual physical activity or decreases in sedentary behaviour were less clear. Concluded although VRT may elicit some health benefits in special populations, there

			is not sufficient evidence to recommend VRT as a means of increasing daily physical activity.
Mitchell et al. (2012)	Effectiveness of VRT on physical activity capacity and performance in children with early brain injuries (TBI/ABI) including CP	4	Overall limited conclusions were reported about the effect of VRT on physical activity in children with early brain injuries including cerebral palsy at this stage, although noted the evidence for typically developing children is promising. Highlighted the need for future high-quality research into the effectiveness of VRT interventions in children and adolescents with cerebral palsy would benefit from the inclusion of measures of physical activity capacity and performance to confirm this.
Monge Pereira et al. (2014)	Impact of VRT in improvement and acquisition of functional skills in children with CP	13	Acknowledged the limitations of the evidence including the limited number of patients enrolled, clinical diversity and age range, as well as the methodological quality of existing trials. Though concluded VRT is a promising tool in the treatment of children with cerebral palsy. Reported there is strong scientific evidence of an acceptable recommendation for the use of VRT systems in the treatment of cerebral palsy.
Ravi et al. (2017)	Effectiveness of VRT rehabilitation for children and adolescents with cerebral palsy	31	Suggested VRT is a promising intervention to improve balance and motor skills in children with cerebral palsy.
Sandlund et al. (2009)	Effectiveness of VRT in rehabilitation of children with sensorimotor disorders	16	Thirteen studies presented positive findings. Three (2 RCTs and 1 Level III study) showed no significant improvements. Concluded VRT is a potentially promising tool for the motor rehabilitation of children but the level of evidence is too limited to assess its value fully.

* Please note the naming of VRT is different across the reviews (e.g. VR – virtual reality, ICP – interactive computer play, SG – serious gaming, AVG – active video gaming)

The two most recent systematic reviews examining VRT in children both focus on children with cerebral palsy and present a meta-analysis of randomised controlled trials (Chen et al. 2018, Ren & Wu (2019). Chen et al. (2018) included 19 RCTs which involved 504 participants. VRT dosage ranged from 8 to 80 hours, sessions varied from 20 to 90 minutes, with frequency from once per week to 7 days per week and length of intervention from 4 to 20 weeks. A medium effect on body structure and function, a large effect on activity components and a small effect on the participation component was reported. In particular, a large effect on arm function and postural control was identified. The authors also reported that bespoke systems

were more effective than commercially available systems. Ren and Wu (2019) focused on the effectiveness of VRT on gross motor skills in children with CP, with strict inclusion criteria and nine papers were reviewed, with a total number of 404 participants. Four of these studies were not reviewed in the Chen et al. (2018) systematic review (including two papers published in 2019). Again, the authors reported a wide variation in overall dose ranging from 6.6 to 40 hours, session length ranged from 17 to 40 minutes, frequency from twice to 7 times per week, and length of intervention from 4 to 9 weeks. The authors concluded that VRT can enhance gross motor skills of children with CP to some extent but called for higher quality RCTs in the future.

A further review by Juras et al. (2019) focuses on the effect of VRT in improving balance specifically, which is of relevance when considering the use of VRT in children with ataxia, although this review is across children and adults with neurological conditions. Twenty studies met the inclusion criteria (assessed using the PEDro assessment with scores ranging from 5 to 8 (PEDro 1999). Again, there was a wide variety in dosage, with session length varying from 20 to 90 minutes, from twice a week to daily, and intervention lasting from 3 to 12 weeks. The authors concluded that VRT appeared to demonstrate better results than both conventional rehabilitation and no intervention but noted the low quality of studies.

It is noted across all the review papers that many of the studies include VRT in addition to routine rehabilitation or compared with no intervention thus any conclusions about the use of VRT as a stand-alone intervention should be interpreted with caution. A study by Taracki et al. (2016) (included in the Juras et el 2019 review), is one of the few studies to have a direct comparison group, with 30 children with CP (age range 5-18 years) randomised to either conventional balance training or VRT training (both in addition to usual care of NDT), in a 24 session programme conducted over 12 weeks. Both groups demonstrated an improvement,

but for children in the VRT group statistically significant improvements were found compared with the 'control' group in all balance tests and WeeFIM score.

Studies that examined VRT specifically in children with ataxia were reviewed in Chapter 3. Children with acquired brain injury (ABI) may present with similar impairments as children with PFT. Historically, although often placed in different categories in the literature, evidence in both ABI and brain tumours should be considered, as tumours (or treatment of) are causal pathology which can result in ABI. For this reason, it is useful to evaluate the literature in this field for further insights into the potential effectiveness and application of VRT. Tatla (2012) reported positive effects of the Nintendo Wii on balance (utilising Timed up and Go (TUG), modified functional reach test (MFRT), Wii Balance board measurements and PEDI as outcome measures) over a 4-week intervention period, with 30-minute sessions on the Wii five times a week, using a single subject design in three children with ABI. In a single case study Cheung (2013) used both the Xbox Kinect and the Wii to improve balance (using the TUG, MFRT, PEDI and Wii balance board as a measure of static balance) in a 10-year-old boy with an ABI (arteriovenous malformation) over fifteen days (30-minute sessions, five times a week). Both these studies included children less than twelve months post injury, therefore natural recovery may also have influenced the results. De Kloet et al. (2012) completed a study where the majority (78%) of participants (aged 8-29 years of age) were over 2 years post acquired or traumatic brain injury. Participants undertook an individualised 12-week programme using the Wii, with a significant change in visual motor coordination reported, however, no change in quality of life (Peds QL) or participation measures were reported (CAPE). A larger study has recently been published by Baque et al. (2017) who describe a RCT (n=30 each group) comparing the efficacy of a web-based gaming programme (Mitii™) on motor performance in children with ABI (age range 8-16 years). The individual diagnoses of the children were not reported in the baseline characteristics therefore it is not possible to determine if any children with brain tumours (or acquired cerebellar pathologies) were included

in the sample. After a 20-week training programme (30 minutes per day, 6 days a week, total training time of 60 hours), significant improvements in functional strength tests were reported but there were no significant differences in secondary outcome measures (6MWT and TUG).

Overall, VRT is a feasible intervention for children aged 4-18 years of age with a range of health conditions and could be considered as a promising tool for improving outcomes in this population. However, further high-quality studies are needed to determine its value in children with PFT.

Appendix 14 – Workshop plan and facilitator guidance

Time	Activity				Equipment
1500-1515	**Greet and consent** (All) (Breakout table available with activities/crafts for those waiting) *Issue participants with expenses forms				Consent forms Expenses forms Breakout table equip (pens/paper/stickers)
1515-1520	**Introduction** (HH) (Inform group of overall aim – help with choosing X Box game for use in upcoming trial. Suitability/engagement/therapeutic value/practicality)				
1520-1530	**'Ice breaker' - Badge making** (All) (Participants make own name badges utilising pictures/stickers of characters/activities on potential games)				Badges Stickers/pictures of gaming characters
1530-1540	**Tour** (Tour of innovation hub, see 3D printer/virtual reality room)				
1540-1545	**Introduce work stations (HH)** (Aims; pick 2 games to play and tell us what you think about them. Tell us what you like/don't like about gaming, try MIRA – tell us what you think about this) SPLIT INTO 2 GROUPS, GROUP 1 – does station 1 followed by station 2 GROUP 2 – does station 3 followed by station 4 SWITCH AFTER BREAK) (dependent on number of participants – expand or collapse this)				
1545-1610	**Station 1** (RK) X Box gaming participation (3 min per game can move between station 1 and 2 to	**Station 2** Rank games played	**Station 3** (BC) 10-12' Discussion about gaming	**Station 4** (MIRA) 10-12' MIRA gaming company	Flip charts and pens Dictaphones x4 X Box x2 Kinect sensor x2 Kinect games MIRA set up

	rank game to minimise waiting)				
1610-1625	**BREAK**				Refreshments
1625-1650	**Station 1** (RK) X Box gaming participation	**Station 2** Rank games played	**Station 3** (BC) Discussion about gaming	**Station 4** (MIRA) MIRA gaming company	As above
1650-1705	**Final Feedback** (HH) (Aim; rank games under remit of suitability; engagement; therapeutic value; practicality – use stickers on flip charts) - Summarise feedback received				Flip chart/pens/stickers
1705-1710	**Close and Certificate** (invite to next workshop)				Certificates

Facilitator Guidance

Overall objectives;

1) From preselected set of Kinect games which would be the most engaging for children and suitable for use?
2) Explore the practicality of using Kinect (and software) in clinic and home setting

Achieve this through ranking and rationale for;

Level of **engagement**

Practicality of use in the **home** setting

Practicality of use in the **clinic** setting

Utility regarding **therapeutic value**

Station 1 (RK)	**Station 2**	**Station 3** (BC)	**Station 4** (MIRA)
X Box gaming participation Each participant to try 2 games	Rank games played Rank games (use number 1-5/smiley face dependent on age) on; Engagement (most fun? Like to play again, hold attention, ?too difficult/too easy) Practicality (ok to play at home/clinic – e.g. space needed, ease to set up) Therapeutic value (adjustability, ?focus on cardio/balance/task specific training, wide age range)	Discussion about gaming Which games enjoy the most? Type; Sport/Explorer/Dance/Combat Difficulty; Systematically harder/increase in scores/rewards for levels/play against people Would you play game if thought would help your balance? What makes you not want to play a game again?	MIRA gaming company Rank games (use number 1-5/smiley face dependent on age) on; Engagement (most fun? Like to play again, hold attention, ?too difficult/too easy) Practicality (ok to play at home/clinic – e.g. space needed, ease to set up) Therapeutic value (adjustability, ?focus on cardio/balance/task specific training, wide age range)

Appendix 15 – FREC approval Phase 3 and Phase 4

Edge Hill University

Helen Hartley 11th October 2017

Dear Helen,

Thank you for submitting your research ethics application '*The ASessment of Physiotherapy managEment for Children with ataxia following surgical resection of posterior fossa Tumour (ASPECT Study)*' (FOHS 189) to the Faculty of Health & Social Care Research Ethics Committee.

I have pleasure in informing you that the Committee recommended that your study is granted Faculty of Health & Social Care research ethics approval, subject to the following conditions:

1. Ethical approval covers only the original study for which it is sought. If the study is extended, changed, and / or further use of samples or data is needed the Committee Administrator, Daniel Brown, must be contacted for advice as to whether additional ethical approval is required.

2. (NHS studies only) NHS Research governance processes must be adhered to. An application must be made to the HRA for approval for the research to be conducted in the NHS. All NHS R&D departments (in Trusts where data is being collected) will also need to be approached for Trust permission to proceed.

3. If the project requires HRA approval and/or NHS ethical approval, please forward evidence of the approval(s) to Daniel Brown (browdan@edgehill.ac.uk) before commencing the study

4. The Principle Investigator is responsible for ensuring that all data are stored and ultimately disposed of securely in accordance with the Data Protection Act (1998) and as detailed within the approved proposal.

5. The Principle Investigator is responsible for ensuring that an annual monitoring form and an end of study form, where appropriate, is sent to the Committee Administrator (browdan@edgehill.ac.uk). The form will be sent to you at the appropriate time by the Committee Administrator.

6. Ethical approval for this research will expire on 31/12/2020. Any extensions to this date will require additional approval from the committee.

The study documentation that has been reviewed and approved is detailed below:

<doc title>	<version no & date>

Research Proposal	V1.1, 01/10/2017
ASPECT WP3+4 Protocol	V1.1, 01/10/2017
ASPECT WP3 Child Assessment Workshop 1	V1.1, 01/10/2017
ASPECT WP3 Child Assessment Workshop 2	V1.1, 01/10/2017
ASPECT WP3 Child Assessment Workshop 3	V1.1, 01/10/2017
ASPECT WP3 Clinical Flyer	V1.0, 11/08/2017
ASPECT WP3 Parent consenting for their child workshop 1	V1.1, 01/10/2017
ASPECT WP3 Parent consenting for their child workshop 2	V1.1, 01/10/2017
ASPECT WP3 Parent consenting for their child workshop 3	V1.1, 01/10/2017
ASPECT WP3 Parent-clinician consent workshop 1	V1.1, 01/10/2017
ASPECT WP3 Parent-clinician consent workshop 2	V1.1, 01/10/2017
ASPECT WP3 Parent-clinician consent workshop 3	V1.1, 01/10/2017
ASPECT WP3 Participant Flyer	V1.1, 01/10/2017
ASPECT WP3 PIS Clinician	V1.0, 11/08/2017
ASPECT WP3 PIS 4-6 years	V1.0, 11/08/2017
ASPECT WP3 PIS 7-10 years	V1.0, 11/08/2017
ASPECT WP3 PIS 11-15 years	V1.0, 11/08/2017
ASPECT WP3 PIS 16-18 years	V1.0, 11/08/2017
ASPECT WP3 PIS Parents	V1.0, 11/08/2017
ASPECT WP3 Workshop Invitation	V1.0, 11/08/2017
ASPECT WP3 Young person consent workshop 1	V1.1, 01/10/2017
ASPECT WP3 Young person consent workshop 2	V1.1, 01/10/2017
ASPECT WP3 Young person consent workshop 3	V1.1, 01/10/2017
ASPECT WP4 Generic Assent	V1.0, 11/08/2017
ASPECT WP4 Generic Consent 16+	V1.0, 11/08/2017
ASPECT WP4 Generic Diary	V1.0, 11/08/2017
ASPECT WP4 Generic Embedded Qualitative Component Questions and Prompts	V1.0, 11/08/2017
ASPECT WP4 Generic Exit Interview Questions and Prompts	V1.0, 11/08/2017
ASPECT WP4 Generic Parent consent for their child	V1.0, 11/08/2017
ASPECT WP4 Generic Parent Consent	V1.0, 11/08/2017
ASPECT WP4 Generic PIS Parents	V1.1, 01/10/2017
ASPECT WP4 Generic PIS 4-6 years	V1.0, 11/08/2017
ASPECT WP4 Generic PIS 7-10 years	V1.0, 11/08/2017
ASPECT WP4 Generic PIS 16-18 years	V1.1, 01/10/2017
ASPECT WP4 Generic Training Plan	V1.0, 11/08/2017
ASPECT WP4 Introduction Letter	V1.0 14/08/2017
ASPECT WP4 PIS Generic 11-15	V1.1, 01/10/2017

Yours sincerely

Professor Mary O'Brien

Chair of Faculty of Health & Social Care Research Ethics Committee
Edge Hill University
St Helens Road
Ormskirk
Lancashire
L39 4QP
obrienm@edgehill.ac.uk

Appendix 16 – REC approval Phase 3 and Phase 4

Health Research Authority

North West - Liverpool East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

22 February 2018

Miss Helen Hartley
Physiotherapy Department
Alder Hey Childrens NHS Foundation Trust
Eaton Road, Liverpool
Liverpool
L12 2AP

Dear Miss Hartley

Study title:	**The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour**
REC reference:	**17/NW/0649**
IRAS project ID:	**227917**

Thank you for your submission of 06/02/2018, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Alternate Vice-Chair and Committee Member.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [ASPECT WP3 Participant Flyer]	Version 1.3	01 February 2018
Copies of advertisement materials for research participants [ASPECT WP3 Clinician Flyer]	Version 1.3	01 February 2018
Covering letter on headed paper [ASPECT Covering Letter]		17 October 2017
Interview schedules or topic guides for participants [ASPECT WP4 Qualitative Questions]	Version 1.0	11 August 2017
Interview schedules or topic guides for participants [ASPECT WP4 Exit Interview]	Version 1.0	11 August 2017
IRAS Application Form [IRAS_Form_24102017]		24 October 2017
Letter from funder [ASPECT NIHR Agreement]		19 January 2017
Letters of invitation to participant [ASPECT WP4 Introduction Letter]	Version 1.0	14 August 2017
Letters of invitation to participant [ASPECT WP3 Invitation]	Version 1.1	16 November 2017
Letters of invitation to participant [ASPECT WP4 Introduction Letter]	Version 1.1	16 November 2017
MHRA Notice of No Objection Letter (Medical Devices) and relevant correspondence [MHRA Correspondance]		04 February 2018
Other [Response to Validation]		31 October 2017
Participant consent form [ASPECT WP3 Assent]	Version 1.3	16 November 2017
Participant consent form [ASPECT WP3 Parent consent for child]	Version 1.3	16 November 2017
Participant consent form [ASPECT WP3 Parent/Clinician Consent]	Version 1.3	16 November 2017
Participant consent form [ASPECT WP3 Young Person Consent Workshop 1]	Version 1.3	16 November 2017
Participant consent form [ASPECT WP4 Assent]	Version 1.1	16 November 2017
Participant consent form [ASPECT WP4 Parent consent for child]	Version 1.1	16 November 2017

Participant consent form [ASPECT WP4 Parent Consent]	Version 1.1	16 November 2017
Participant consent form [ASPECT WP4 16-18 Consent]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 4-6]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 7-10]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 11-15]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 16-18]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS Parent]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS Clinician]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 4-6]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 7-10]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 11-15]	Version 1.2	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 16-18]	Version 1.2	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS Parent]	Version 1.2	16 November 2017
Referee's report or other scientific critique report [ASPECT NIHR Panel Feedback]		19 May 2017
Research protocol or project proposal [ASPECT Research Protocol]	Version 1.1	01 October 2017
Sample diary card/patient card [ASPECT WP4 Diary]	Version 1.0	11 August 2017
Sample diary card/patient card [ASPECT WP4 Training Plan]	Version 1.0	11 August 2017
Summary CV for Chief Investigator (CI) [CI CV]		12 October 2017
Summary CV for supervisor (student research) [ASPECT Supervisor CV]		20 October 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [ASPECT WP4 CONSORT Diagram]	Version 1.0	22 July 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

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 R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

17/NW/0649	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

On Behalf Of
Peter Walton
Alternate Vice-Chair

Email:nrescommittee.northwest-liverpooleast@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Miss Lucy Cooper, Alder Hey Children's Hospital NHS Foundation Trust*

Appendix 17 – HRA approval Phase 3 and Phase 4

NHS
Health Research Authority

Miss Helen Hartley
Physiotherapy Department
Alder Hey Children's NHS Foundation Trust
Eaton Road, Liverpool
Liverpool
L12 2AP
helen.hartley@alderhey.nhs.uk

Email: hra.approval@nhs.net

5 March 2018

Dear Miss Hartley,

Letter of HRA Approval

Study title:	**The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour**
IRAS project ID:	**227917**
REC reference:	**17/NW/0649**
Sponsor	**Alder Hey Childrens NHS Foundation Trust**

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 the HRA website.

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, 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.

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 through IRAS.

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.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is 227917. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Lucy Cooper, Alder Hey NHS Foundation Trust [Sponsor Contact & Lead NHS R&D Contact]*
research@alderhey.nhs.uk

IRAS project ID	227917

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [ASPECT WP3 Participant Flyer]	Version 1.3	01 February 2018
Copies of advertisement materials for research participants [ASPECT WP3 Clinician Flyer]	Version 1.3	01 February 2018
Covering letter on headed paper [ASPECT Covering Letter]		17 October 2017
HRA Schedule of Events	1	08 November 2017
HRA Statement of Activities	1	08 November 2017
Interview schedules or topic guides for participants [ASPECT WP4 Qualitative Questions]	Version 1.0	11 August 2017
Interview schedules or topic guides for participants [ASPECT WP4 Exit Interview]	Version 1.0	11 August 2017
IRAS Application Form [IRAS_Form_24102017]		24 October 2017
Letter from funder [NIHR Funding Details]		
Letter from funder [ASPECT NIHR Agreement]		19 January 2017
Letters of invitation to participant [ASPECT WP3 Invitation]	Version 1.1	16 November 2017
Letters of invitation to participant [ASPECT WP4 Introduction Letter]	Version 1.1	16 November 2017
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Participant consent form [ASPECT WP4 Parent consent for child]	Version 1.1	16 November 2017
Participant consent form [ASPECT WP4 Parent Consent]	Version 1.1	16 November 2017
Participant consent form [ASPECT WP4 16-18 Consent]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 4-6]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 7-10]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 11-15]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS 16-18]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS Parent]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP3 PIS Clinician]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 4-6]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 7-10]	Version 1.1	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 11-15]	Version 1.2	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS 16-18]	Version 1.2	16 November 2017
Participant information sheet (PIS) [ASPECT WP4 PIS Parent]	Version 1.2	16 November 2017
Referee's report or other scientific critique report [ASPECT NIHR Panel Feedback]		19 May 2017
Research protocol or project proposal [ASPECT Research Protocol]	Version 1.1	01 October 2017

IRAS project ID	227917

Sample diary card/patient card [ASPECT WP4 Diary]	Version 1.0	11 August 2017
Sample diary card/patient card [ASPECT WP4 Training Plan]	Version 1.0	11 August 2017
Summary CV for Chief Investigator (CI) [CI CV]		12 October 2017
Summary CV for supervisor (student research) [ASPECT Supervisor CV]		20 October 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [ASPECT WP4 CONSORT Diagram]	Version 1.0	22 July 2017

IRAS project ID	227917

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Lucy Cooper (sponsor contact)	Helen Hartley (Chief Investigator)
Tel: 0151 252 5570	0151 252 5660
Email: lucy.cooper@alderhey.nhs.uk;	helen.hartley@alderhey.nhs.uk;

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	As part of the applicant's response to provisional opinion to REC, updated participant information sheets and consent/assent forms were submitted to comply with HRA Standards.
3.1	Protocol assessment	Yes	No comments.
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	There are two site types participating in this study. A statement of activities and schedule of events are not required for site type 1 as this organisation is also the study sponsor.

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			The sponsor has however submitted a statement of activities and schedule of events as the agreement for participating NHS sites acting as site type 2 in the study. The sponsor has confirmed no other form of agreement is required, or will be used.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study.
4.3	Financial arrangements assessed	Yes	The study is funded by the NIHR. The sponsor has confirmed that funding will be provided to participating NHS sites, as detailed in the Statement of Activities. A copy of the funding evidence indicating the level of funding has been provided.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	As per 2.1 above, as part of the applicant's response to provisional opinion to REC, updated participant information sheets and consent/assent forms were submitted to comply with The Data Protection Act.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion	Yes	REC Favourable Opinion was issued on 22 February 2018.

Section	HRA Assessment Criteria	Compliant with Standards	Comments
	received for applicable studies		
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There are two site types participating in this study. Study activity at each participating NHS site type is as follows:

- Site Type 1 – Host Organisation: this organisation will recruit and consent participants, and undertake all study activities in respect of both Work Packages 3 and 4.

- Site Type 2 – WP3 - PIC Activity & WP4 – All Activities: these organisations will:

  In respect of Work Package 3, undertake eligibility checks and carry out the mail out of study introduction letters.

  In respect of Work Package 4, will recruit and consent participants, and undertake all study activities.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If Chief Investigators, sponsors or Principal Investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the Chief Investigator, sponsor or Principal Investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Confirmation as to whether formal confirmation of capacity and capability is expected from participating NHS sites in England is as follows:
 	
• **Site Type 1 – Host Organisation**: The R&D office will confirm to the CI when the study can start.
 	
• **Site Type 2 – WP3 - PIC Activity & WP4 – All Activities**: - Participating NHS organisations in England **will be expected to formally confirm their capacity and capability** to host this research.
 	
  • The sponsor should ensure that participating NHS organisations are provided with a copy of this letter and all relevant study documentation, and work jointly with NHS organisations to arrange capacity and capability whilst the HRA assessment is ongoing.
  • Further detail on how capacity and capability will be confirmed by participating NHS organisations, following issue of the Letter of HRA Approval, is provided in the *Participating NHS Organisations* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections of this appendix.
  • The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Local Principal Investigator is required at both site types, and these have already been identified. **Training** – The sponsor will provide a site initiation visit to the local research team, and one training session on assessment measures for local therapists. In addition, in line with local policy, staff must be suitably trained / experienced. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
In respect of HR Good Practice Guidelines, the following arrangements are expected at both site types:

Local staff with existing contractual arrangements in place with the participating NHS site, are not expected to require additional access arrangements.

Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant (such as consent process), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm DBS checks and occupational health clearance.

For research team members undertaking activities that do not impact on the quality of care of the participant (for example, administering questionnaires), a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

- The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.
- The participants randomised to the intervention arm of the feasibility trial will be loaned an X Box Kinect with selected game for the duration of their 4 week home training programme, to be returned to the sites after this 4 week period. A log will record this. The sponsor has confirmed it has suitable indemnity arrangements in place to cover the equipment.

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Workshop information sheet to help parents explain to children 4-6 years of age (or children who may have difficulty reading the participant information leaflets)

The following prompts may be useful in explaining the study to your child

Who else is helping?

They are asking lots of other children their parents and other physios to help too.

What do I have to do?

They will ask you to come to the hospital and try some X Box games and tell us if you like them.

Who do I talk to?

If you are worried about anything then you can tell me about it and I will talk to the physios or the doctors or the people doing the project.

Do I have to take part?

No, you don't have to take part. If you don't want to be in the project you can tell me and I will talk to the people doing the project.

The people doing the project say thank you for your help.

Appendix 19 - PIS ASPECT WP3 Age 7-10

Will anyone else know that I'm doing this?

Your mum/dad/carer will know that you are taking part and the physios who are helping to run the workshops.

What if I have some questions?

If you have any questions about the workshops please talk to your parents/mum/dad/carer and they can contact Helen Hartley at Alder Hey Hospital or Ally Hollingworth at Royal Manchester Children's Hospital.

Thank you for thinking about joining in the workshops.

INSERT SITE LOGO

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Workshop Information Sheet for Children aged 7- 10 years

Introduction

ASPECT WP3 Workshop Participant Information Sheet 7-10 years Version 1.1 Dated 16.11.2017 IRAS ID 227917

Introduction

Hello. My name is Helen Hartley.

I am asking you if you would like to take part in some workshops.

Before you decide if you want to take part, you need to know why I am doing the workshops and what will happen.

What are the workshops about?

The workshops are about physiotherapy for children like you who are a bit wobbly when they stand up or walk around. We want to plan a project about this in the future.

Why have I been asked to take part?

We are asking children like you who have some problems with being a bit wobbly when you are walking to take part in the workshops.

Your mum/dad/carer have said it is OK for you to take part if you want to.

Do I have to join in the workshops?

No! It's up to you whether you join in the workshops. If you decide to join in and then you change your mind, that is OK.

What will happen if I join in?

You will take part in workshops about using X Box to help with your physiotherapy.

We would like you to try some games and then tell us;
If you like playing the games?
Which you like best
Which bits you don't like about them

What are the good things about taking part?

We hope that you will enjoy taking part. We hope that this project might help us help other children.

Are there any bad things about taking part?

We don't think there are any bad things about taking part.

Being part of the workshops will mean 1 or 2 extra visits to the hospital.

Appendix 20 – PIS ASPECT WP3 Age 11-15

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more about the workshops. If new information becomes available during this project your physiotherapist will discuss it with you.

What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Chief Investigator (Helen Hartley 0151 252 5236).

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk.
You may also wish to contact the hospital complaints department on 0151 252 5913.

Many thanks for taking the time to read this information sheet

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Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Workshop Information Sheet for Young People aged 11-15 years

Introduction

ASPECT WP3 Workshop Participant Information Sheet 11-15 years
Version 1.1 Dated 16.11.2017 IRAS ID 227917

Introduction

You are being invited to take part in some workshops as part of a research project. Before you decide if you want to take part, you need to know why we are doing the project and what will happen. This information sheet tells you what the workshops are about.

What are the workshops about?

The workshops are about using the X Box Kinect as part of physiotherapy. We are planning a study in the future to look at how X Box gaming can support physiotherapy and want to use these workshops to help plan parts of this future study.

Who is doing the study?

The main person doing the project is Helen Hartley. She is a physiotherapist who works at Alder Hey Children's Hospital. This study is part of the work she is doing at Edge Hill University for her PhD. She is working with other physiotherapists and doctors/nurses at Alder Hey and Royal Manchester Children's Hospital who will help with the workshops. Her study is being supervised by a team of researchers.

Why have I been asked to take part?

You have had treatment for a posterior fossa tumour (in the back part of your brain) and you have some problems with balance/co-ordination. Your mum/dad/carer have said it is okay for you to take part if you want to.

Do I have to take part?

No! It is up to you whether you take part in the workshops. If you do take part, you can change your mind, without telling us why and no one will mind. Your decision will not affect your care.

What will happen if I take part?

The workshops will be in place where you can share your ideas about using the X Box Kinect to help with physiotherapy. There will be a range of activities e.g. ask you to rank the games in order of which you liked best. The ideas you generate will be written on postcards. There will be plenty of breaks and food/drinks will be provided. We will be holding 3 workshops in total. They will be held in the Innovation Hub at Alder Hey Hospital.

Workshop 1 + 2 (on the same day, lasting around 2-2.5 hours)

As part of workshop 1+2 we will ask you:

- which games you enjoy best to work on your balance
- how easy is it to practice the games in the hospital
- how easy is it to practice the games at home

Workshop 3 (held a few weeks later, lasting around 1-1.5 hours)

As part of workshop 3 we will ask you to help us find out:

- what other software can be used with the Kinect to help with studies
- what would be the best type of gaming to use in studies

What are the good things about taking part?

We hope that you will enjoy taking part. What we find out will help us to plan a study on using the X Box to support physiotherapy in the future.

Are there any bad things about taking part?

We don't think there are any bad things about taking part. However, it will mean up to 2 extra visits to the hospital.

Will anyone else know that I'm doing this?

Your mum/dad/carer will know that you are taking part and the physios/doctors/nurses who are helping to run the workshops. We will not tell anyone else and no-one will know what you have told us afterwards unless you tell us something which makes us think you are being harmed by someone. If we write anything up about the study, your name and other details will not be shared.

Appendix 21 - PIS ASPECT WP3 Age 16-18

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Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Workshop Information Sheet for Young People (aged 16-18 years)

Project Team

Helen Hartley – Paediatric Physiotherapist, Alder Hey Hospital
Prof Barry Pizer – Consultant Oncologist, Alder Hey Hospital
Dr Ram Kumar – Consultant Paediatric Neurologist, Alder Hey Hospital
Prof Bernie Carter – Professor of Children's Nursing, Edge Hill University
Dr Lisa Bunn – Lecturer in Physiotherapy, Plymouth University
Dr Elizabeth Cassidy – Physiotherapist, Researcher

Introduction

Thank you for reading this information sheet. You are being invited to take part in a series of workshops as part of a research project. Before you make your decision, it is important for you to understand why this project is being done and what it will involve. Please take your time to read the following information carefully. If anything is not clear to you, or if you would like more information then please feel free to ask a member of the research team, whose details are at the end of this sheet. Please take time to decide whether or not you wish to take part.

Who is doing this research?

Therapists from the acute neuro-physiotherapy team at Alder Hey Hospital with support from the Neuro-oncology team, Professor Bernie Carter (Edge Hill University), Physiotherapists from Royal Manchester Children's Hospital and the Innovation Hub at Alder Hey Hospital. The Principal Investigator is Helen Hartley, a Specialist Paediatric Physiotherapist. This study forms part of Helen's PhD studies which are funded by a NIHR (National Institute for Health Research) fellowship.

What is the aim of the workshops?

The most common movement problem reported in children and young people with brain tumours is co-ordination and balance problems, which are known as ataxia. There are currently no guidelines on how much physiotherapy or which type is best for ataxia in children/young people following surgery for posterior fossa tumours.

We are planning a trial in the future to examine virtual training (e.g. X Box Kinect to support physiotherapy) in children and young people with ataxia following surgical resection of posterior fossa tumour and we would like to use these workshops to help us plan parts of the upcoming trial.

Why have I been chosen?

Every child and teenager (up to the age of 18) who has or has had balance/co-ordination problems following surgery for a posterior fossa tumour are eligible to take part in the workshops.

Do I have to take part?

No, taking part is entirely voluntary. If you decide to take part you can attend one workshop or all of them. You can join in as much as you like. If you do not wish to take part you don't have to, and you can change your mind at any point. A decision to not take part or stop taking part at any point will not affect the standard of care given to you. If you decide to stop taking part at any point, any information collected up to this point will be kept, however, nothing further will be collected.

What will happen if I decide to take part in the workshops?

If you are interested in taking part in the workshops the Principal Investigator (Helen Hartley) will contact you/your parents via email/telephone (with your agreement) to confirm the dates/times of the workshops.
The workshops will be a place where you can share your ideas and views about X Box Kinect as part of physiotherapy with each other and the clinicians and researchers.

There will be a range of activities e.g. we might ask you to rank the games in order of preference. You can contribute as much as you like. The ideas and views you generate will be documented on postcards. There will be plenty of breaks also and refreshments will be provided.

Workshop 1 and 2 will be held on the same day and aim to answer the following questions:
What games would children/young people enjoy best that work on their balance?
How practical is it to use to virtual training in the hospital?
How practical is it to use to virtual training at home?

Workshop 3 will be held a few weeks after and will aim to answer these questions:
What other software is available that could link with the Kinect that might be of use for research?
What would be the best type of virtual training to use in research?

Please note the virtual training will not continue after the workshops have been completed.

Are there any benefits to me taking part?

We hope that you will enjoy the workshops though there will not be any direct benefit from taking part. We hope that what we learn from the workshops will help us plan a research study in the future.

Are there any disadvantages or risks involved in my participation in these workshops?

Apart from the extra visits to the hospital we do not think there are any disadvantages to you taking part in the workshops.
The time commitments will be as follows;
Workshop 1 and 2 will run on the same day with breaks in between and last 2-2.5 hours in total.
Workshop 3 will take place a few weeks later and will last approximately 1.5 hours. It would be great if you can attend both workshops but it is ok if you can only attend one.

As part of the workshops you will be able to try the games under supervision.

What will happen with the information I produce?

When discussing issues in the workshop other participants will see and hear what you are saying. However, when we produce a report of the findings no names or specific details will be included. Data stripped of any personally identifying details collected during the workshops may be looked at by individuals from regulatory authorities (such as the National Institute of Health Research) or from the NHS Trust. Once the study is complete all personal information will be securely stored (encrypted and password protected on a non-mobile device within Alder Hey Children's NHS Foundation Trust) for up to 6 months by the lead researcher (e.g. contact details). At 6 months all of the non-identifiable information will be kept for a total of 10 years in line with Alder Hey Children's Foundation Trust procedures for handling, processing, storage and destruction of data and the Data Protection Act 1998.

How can I claim my expenses?

Costs related to additional visits can be reimbursed. Acceptable expenses include; standard class train/bus tickets, mileage at 40p per mile and car parking. Please provide information and receipts where possible to the research team.

What will happen to the results of the workshops?

The results of the workshops will be shared with the research team (you will not be able to be identified in the report) and be used to help plan a trial testing virtual training in children with ataxia following surgical resection of brain tumour. The trial will begin in 2018.

Who is funding the workshops?

The funding for the workshops is coming from the National Institute of Health Research who are funding Helen Hartley's Clinical Doctoral Fellowship (ICA-CDRF-2016-02-065). The other members of the research team will not receive any personal payments for undertaking this research.

Who has reviewed the workshops?

The workshops have been reviewed by the Faculty of Health and Social Care Research Ethics Committee at Edge Hill University and by the National Research Ethics Service (committee details and numbers to be added).

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain, or have concerns about any aspect of the way you have been treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more.

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Chief Investigator (Helen Hartley 0151 252 5236) or you can contact Helen's Director of Studies, Professor Bernie Carter via email bernie.carter@edgehill.ac.uk or phone 01695 657771

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk.

You may also wish to contact the hospital complaints department on 0151 252 5913.

Many thanks for taking the time to read this information sheet

Appendix 22 - PIS ASPECT WP3 – Parent information sheet

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Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Workshop Information Sheet for Parents

Project Team

Helen Hartley – Paediatric Physiotherapist, Alder Hey Hospital
Prof Barry Pizer – Consultant Oncologist, Alder Hey Hospital
Dr Ram Kumar – Consultant Paediatric Neurologist, Alder Hey Hospital
Prof Bernie Carter – Professor of Children's Nursing, Edge Hill University
Dr Lisa Bunn – Lecturer in Physiotherapy, Plymouth University
Dr Elizabeth Cassidy – Physiotherapist, Researcher

Introduction

Thank you for reading this information sheet. You and your child are being invited to take part in a series of workshops as part of a research project. Before you make your decision, it is important for you to understand why this project is being done and what it will involve. Please take your time to read the following information carefully. If anything is not clear to you, or if you would like more information then please feel free to ask a member of the research team, whose details are at the end of this sheet. Please take time to decide whether or not you wish to take part.

Who is doing this research?

Therapists from the neuro-physiotherapy team at Alder Hey Hospital with support from the Neuro-oncology team, Professor Bernie Carter (Edge Hill University), Physiotherapists at Royal Manchester Children's Hospital, and the Innovation Hub at Alder Hey Hospital. The Principal Investigator is Helen Hartley, a Specialist Paediatric Physiotherapist. This study forms part of Helen's PhD studies which are funded by a NIHR (National Institute for Health Research) fellowship.

What is the aim of the workshops?

The most common movement problem reported in children with brain tumours is co-ordination and balance problems, which are known as ataxia. There are currently no guidelines on how much physiotherapy or which type is the best for ataxia in children/young people following surgery for posterior fossa tumours.

We are planning a trial in the future to examine virtual training (e.g. X Box Kinect to support physiotherapy) in children with ataxia following surgical resection of posterior fossa tumour and we would like to use these workshops to help us plan parts of the upcoming trial.

Why have we been chosen?

Every child and teenager (up to the age of 18) who has or has had balance/co-ordination problems following surgery for a posterior fossa tumour and their parents are eligible to take part in the workshops.

Do I have to take part and what about my child?

No, taking part is entirely voluntary. If you decide to take part you can attend one workshop or all of them. You can join in as much as you like. If you do not wish to take part you don't have to, and you can change your mind at any point. A decision to not take part or stop taking part at any point will not affect the standard of care given to your child. If you decide to stop taking part at any point, any information collected up to this point will be kept, however, nothing further will be collected.

What will happen if I and/or my child decide to take part in the workshops?

If you are interested in taking part in the workshops the Principal Investigator (Helen Hartley) will contact you via email/telephone (with your agreement) to confirm the dates/times of the workshops.
The workshops will be a place where you can share your ideas and views of X Box Kinect as part of physiotherapy with each other and the clinicians and researchers.
There will be a range of activities e.g. we might ask you to rank the games in order of preference. You can contribute as much as you like. The ideas you generate will be documented on postcards. There will be plenty of breaks also and refreshments will be provided.

Workshop 1 and 2 will be held on the same day and aim to answer these questions:
What games would the children enjoy best that work on their balance?
How practical is it to use to virtual training in the hospital?
How practical is it to use to virtual training at home?

Workshop 3 will be held a few weeks after and will aim to answer these questions:
What other software is available that could link with the Kinect that might be of use for research?
What would be the best type of virtual training to use in research?

Are there any benefits to us taking part?

We hope that you will enjoy the workshops though there will not be any direct benefit from taking part. We hope that what we learn from the workshops will help us plan a research study in the future.

Are there any disadvantages or risks involved in my child's participation in this study?

Apart from the extra visits to the hospital we do not think there are any disadvantages to your child and you taking part in the workshops.
The time commitments will be as follows;
Workshop 1 and 2 will run on the same day with breaks in between and last 2-2.5 hours in total.
Workshop 3 will take place a few weeks later and will last approximately 1.5 hours. It would be great if you can attend both workshops but it is ok if you can only attend one.

As part of the workshops your children will be able to try the games under supervision.

What will happen with the information we produce?

When discussing issues in the workshop other participants will see and hear what you are saying. However, when we produce a report of the findings no names or specific details will be included. Data stripped of any personally identifying details collected during the workshops may be looked at by individuals from regulatory authorities (such as the National Institute of Health Research) or from the NHS Trust. Once the study is complete all personal information

will be securely stored (encrypted and password protected on a non-mobile device within Alder Hey Children's NHS Foundation Trust) for up to 6 months by the lead researcher (e.g. contact details). At 6 months all of the non-identifiable information will be kept for a total of 10 years in line with Alder Hey Children's Foundation Trust procedures for handling, processing, storage and destruction of data and the Data Protection Act 1998.

How can I claim our expenses?

Costs related to additional visits can be reimbursed. Acceptable expenses include; standard class train/bus tickets, mileage at 40p per mile and car parking. Please provide information and receipts where possible to the research team.

What will happen to the results of the workshops?

The results of the workshops will be shared with the research team (you will not be able to be identified in the report) and be used to help plan a trial testing virtual training in children with ataxia following surgical resection of brain tumour. The trial will begin in 2018.

Who is funding the workshops?

The funding for the workshops is coming from the National Institute of Health Research who are funding Helen Hartley's Clinical Doctoral Fellowship (ICA-CDRF-2016-02-065). The other members of the research team will not receive any personal payments for undertaking this research.

Who has reviewed the workshops?

The workshops have been reviewed by the Faculty of Health and Social Care Research Ethics Committee at Edge Hill University and by the National Research Ethics Service (committee details and numbers to be added).

What if something goes wrong?

If you or your child is harmed by taking part in this research project, there are no special compensation arrangements. If you or your child is harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain, or have concerns about any aspect of the way you have been treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more.

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Chief Investigator (Helen Hartley 0151 252 5236) or you can contact Helen's Director of Studies, Professor Bernie Carter via email bernie.carter@edgehill.ac.uk or phone 01695 657771

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk.

You may also wish to contact the hospital complaints department on 0151 252 5913.

Many thanks for taking the time to read this information sheet

Appendix 23 - Assent ASPECT WP3

INSERT TRUST LOGO

Edge Hill University

Child Assent Form: The ASPECT Study Workshop _____

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)
Name of Researcher: Helen Hartley, Specialist Paediatric Physiotherapist, Alder Hey Hospital

		Please initial box
1.	I have read the information about the study (workshops) or had it read to me	
2.	I understand what the study (workshop) is about and have asked all the questions I want to	
3.	I understand that I do not have to take part and can stop at any time	
4.	I understand that during the workshop we will talk about using the X Box Kinect and other games to help with physiotherapy in hospital and at home	
5.	I know the workshops are happening to help plan future studies in this area	
6.	I understand that my name will not be used in the final report	
7.	I agree to take part in this workshop	

Name of Child	Date	Signature
Name of Person verifying assent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 24 – Consent 16-18 years ASPECT WP3

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Edge Hill University

Young Person (aged 16-18 years) Consent Form
The ASPECT Study
Workshop _____

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: Helen Hartley, Specialist Paediatric Physiotherapist, Alder Hey Hospital

		Please initial box
1.	I confirm that I have read and understand the information sheet dated (version) for the above study (workshops) and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that during the workshops we will share ideas about the use of virtual training (e.g. X Box Kinect gaming) to support physiotherapy in the hospital and at home.	☐
4.	I understand that the reason for the workshops is to help plan future research in this area.	☐
5.	I understand that my name will not be used in the final report or any other materials produced.	☐
6.	I consent to take part in this workshop.	☐

_____	_____	_____
Name of Young Person	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 25 – Parent consent for their child ASPECT WP3

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Edge Hill University

Parent/Carer Consent Form for their child to participate: The ASPECT Study Workshop _____

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: Helen Hartley, Specialist Paediatric Physiotherapist, Alder Hey Hospital

	Please initial box
1. I confirm that I have read and understand the information sheet dated (version) for the above study (workshops) and have had the opportunity to ask questions.	☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐
3. I understand that during the workshops we will talk about using X Box Kinect and other games to help with physiotherapy in hospital and at home and my child will be able to try the games.	☐
4. I know the workshops are happening to help plan future studies in this area.	☐
5. I understand that my child's name will not be used in the final report	☐
6. I agree for my child to take part in this workshop	☐

_____	_____	_____
Name of Parent consenting on child's behalf	Date	Signature
_____	_____	_____
Name of Child	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 26 – Parent/clinician consent ASPECT WP3

INSERT TRUST LOGO

Edge Hill University

Parent/Carer/Clinician Consent Form: The ASPECT Study Workshop _____

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: Helen Hartley, Specialist Paediatric Physiotherapist, Alder Hey Hospital

	Please initial box
1. I confirm that I have read and understand the information sheet dated (version) for the above study (workshops) and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.	☐
3. I understand that during the workshop we will share ideas about the use of virtual training to support physiotherapy in the hospital and at home.	☐
4. I understand that the reason for the workshops is to help plan future research in this area.	☐
5. I understand that my name will not be used in the final report or other materials produced.	☐
6. I consent to take part in this workshop	☐

Name of Participant (Parent/Clinician)	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 27 – GDPR Compliant Information Sheet

GENERAL DATA PROTECTION REGULATION

Study Title	The Assessment and Physiotherapy management of ataxia in children following surgical resection of posterior fossa tumour (ASPECT)
Chief Investigator	Miss Helen Hartley
IRAS Number	227917

As a Trust 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.

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.

Alder Hey Children's NHS Foundation Trust takes great care to abide by our legal and moral obligations when handling your personal and healthcare data. Due to changes introduced in the EU General Data Protection Regulation (GDPR), we are writing to provide you with information on the lawful basis on which we are processing your data. The lawful basis for the processing of your personal data for the research study which you have participated in is a task in the public interest.

The data you have provided will be stored for 10 years. You are free to withdraw your consent for your data to be collected, processed, or stored at any time. However if the data has already been anonymised it will not be possible to withdraw your data.

We will not share your data unless you have provided explicit consent for us to do so.

The data controller for this study is Alder Hey Children's NHS Foundation Trust and the Alder Hey Data Protection Officer can be contacted on info.gov@alderhey.nhs.uk

Alder Hey Children's NHS Foundation Trust strives to maintain the highest standards of rigour in the processing of your data. However, if you have any concerns about the way in which the trust processes your personal data, it is important that you are aware of your right to lodge a complaint with the Information Commissioner's Office.

2018_11_07_V1

Appendix 28 – Flyer for child/parents ASPECT WP3

INSERT SITE LOGO

Edge Hill University

Volunteers Required

A research study* being led by Helen Hartley, Paediatric Physiotherapist at Alder Hey, with the support of the physiotherapists at Royal Manchester Children's Hospital, is looking for volunteers to take part in workshops to help plan studies to work on balance problems in children and young people with posterior fossa tumours.

The research is looking at whether using games such as X Box Kinect games as part of physiotherapy can help children and young people improve their balance and co-ordination.

Information about the workshops

- **When:** March/April 2018
- **Where:** The Innovation Hub at Alder Hey Children's Hospital
- **Who can join in:** Children, teenagers (aged 4-18 years) and parents welcome
- **How many workshops do I take part in:** Up to 3 (1 and 2 held on the same day with a break in between, workshop 3 held a few weeks later)
- **What will happen:** You will be asked to talk to us in groups and try out the games if you want, helping us to see which gaming activities could be used to support physiotherapy
- **What about expenses?** Refreshments + travel expenses available
- **How do I find out more?** Ask the Physios for more information
- **You can also contact;**

Helen Hartley (Physiotherapist at Alder Hey Hospital) 0151 252 5660

Ally Hollingworth (Physiotherapist at RMCH) 0161 701 5438

(*The ASPECT Study: The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour)

WP3 Participant Flyer Version 1.3 01.02.2018 IRAS ID 227917

Appendix 29 – Invitation for workshops ASPECT WP3

INSERT SITE LOGO

Edge Hill University

Invitation to participate in practical workshops about X Box Kinect gaming to support physiotherapy for children and young people following surgery for posterior fossa tumour (The ASPECT Study)

When?

Workshop 1 and 2 XX/XX/XXXX from XXXX – XXXX (with food and breaks!)

Workshop 3 XX/XX/XXXX from XXXX-XXXX

Who?

✓Children and young people (age 4 – 18) with balance problems after surgery for a posterior fossa tumour

✓ Parents and carers of young people with balance problems after surgery for posterior fossa tumour

✓Physios

✓Gaming experts

Where?

The innovation hub at Alder Hey Children's Hospital – ground floor between A and B sections

(exit the main hospital near the blue lifts, entrance is located at the end of the building on the left)

Why?

This is part of a study to find out;

Workshop 1 and 2

Which games the children enjoy and are best to use with the X box Kinect to work on their balance

How practical it is to use the X Box in the hospital as part of a physio programme

How practical it is to use the X Box at home as part of a physio programme

Workshop 3

What other games/computer types could we use for balance exercises?

What games would be the best to use in studies?

How?

You can come to all the workshops or just one. If you can stay for the whole workshop that would be good, but you can stop whenever you want. You can try the games if you want to.

Refreshments and travel expenses are available

It would be helpful if you could let Helen Hartley (0151 252 5660) Helen.hartley@alderhey.nhs.uk know if you plan to come along.

Thank you

ASPECT WP3 Workshop Invitation Version 1.1 16.11.2017 IRAS ID 227917

Appendix 30 - Flyers for physiotherapists ASPECT WP3

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Edge Hill University

Volunteers Required

A research study* being led by Helen Hartley, Paediatric Physiotherapist at Alder Hey with support of the Physiotherapy team at Royal Manchester Children's Hospital, is looking for Clinician volunteers to take part in workshops to help plan studies to work on balance problems in children and young people with posterior fossa tumours.

The ASPECT study is looking at whether using games such as X Box Kinect games as part of physiotherapy can help children and young people improve their balance and co-ordination.

Information about the workshops

- **When:** March/April 2018
- **Where:** The Innovation Hub at Alder Hey Children's Hospital
- **Who can join in:** Children/Parents and Clinicians
- **How many workshops do I take part in:** Up to 3 (1 and 2 held on the same day with a break in between, workshop 3 held a few weeks later)
- **What will happen:** Group discussion/activities and trying out games to help determine what virtual training will be practical to use in future research studies
- **What about expenses?** Refreshments and travel expenses available
- **How do I find out more:** Please contact Helen Hartley 0151 252 5660 or helen.hartley@alderhey.nhs.uk

(*The ASPECT Study: The ASsessment and Physiotherapy managEment of ataxia In Children following surgical resection of posterior fossa Tumour)

Appendix 31 – XBox game analysis (based on KWIC Resource)

	Kinect Adventures				
	Space Pop	**River Rush (Participant and clinician top ranked)**	**Reflex Ridge**	**Rally Ball**	**20,000 Leaks**
Game description	Player moves in space by side stepping, squatting and moving arms to elevate the avatar and then hover over and pop bubbles to obtain pins.	Player stands on a raft leaning forwards and sideways and jumping to navigate down the rapids. If the raft hits a pinwheel gate the player gets pins.	Player stands on rail cart and avoids obstacles by bending and side stepping from side to side, while concurrently collecting pins. Jumping makes the cart go faster.	Player stands in an arcade environment and uses limbs, head and trunk to strike moving balls in order to hit boxes and two kinds of targets in the arcade.	Player stands inside a glass bubble that separates the player from the sea. Using hands, feet, and head player side- steps or lunges to reach and close the leaks that are generated by fish and sharks crashing into the bubble.
Age	Any	Any	Any	Any	Any
Flexible entry (fixed or variable entry points)	Flexible (Beginner, intermediate, advanced)	Flexible (Beginner, intermediate, advanced)	Flexible (Beginner, intermediate , advanced)	Flexible (Beginner, intermediate, advanced)	Flexible (Beginner, intermediate, advanced)
Game Start	Player raises hand.	Player Starts	Player uses arms to pull through the gate.	Player strikes the ball	Player raises hand
Player/Game driven	Game driven**:** Bubbles appear regardless of player movement.	Game driven**:** The raft moves down the river regardless of player movement.	Game driven**:** The rail cart moves forward regardless of player movement.	Game driven**:** Movement of balls is independent of player action.	Player driven**:** The next leak appears only after the previous leak is plugged.
Stability (Maintain a posture/orientation of the trunk and/or limbs)	Yes: Standing	Yes: Standing	Yes: Standing	Yes: Standing	Yes: Standing
Mobility (Movement of body segments to reach a target, avoid obstacles, assume required	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk Head

positions, or to “drive” or “steer” the game task)					
Agility	No	Yes**:** Jumping and side stepping.	Yes**:** Jumping, dodging (with a weight shift), side stepping and squatting.	Yes**:** Side stepping	Yes: Side stepping
Spatial Accuracy (The type of accuracy required for aiming movements for which spatial position of the movement’s end point is important to task performance)	Yes: To pop bubbles.	Yes: To steer and land the raft.	Yes: To avoid obstacles.	Yes: To hit balls and targets.	Yes: To plug leaks.
Game Duration	Consistent	Skill dependent: shortens.	Skill dependent: shortens.	Consistent	Consistent
Cognitive operations (Executive functions of planning, response selection and switching attention)	Planning Switching Attention	Planning Switching attention Response selection	Response selection	Planning Switching Attention	Planning Response selection
Feedback (Information from an external source intended to enhance/replace the intrinsic feedback that comes from a person’s own sensory, visual, and auditory systems)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression (The extent to which the physical and/or cognitive difficulty level of the game progresses within a single trial of game play)	Not within game	Not within game	Yes: Within a level speed and number of obstacles increase.	Yes: More balls appear at faster speeds.	Yes: Within a level greater number of leaks appear over time.
Performance Indicator (Performance indicators	Number of pins collected. Medal	Number of pins collected and time to	Number of pins collected and time to	Number of targets hit. Medal reflects	Number of pins collected. Medal

reflecting a player's success)	reflects game performance .	complete course. Medal reflects game performance .	complete course.	game performance .	reflects game performance .
I**nstructions** (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments	Ref: Taken from KWIC Connecting with Clinicians Resource				

	Carnival Games in Action – Coaster Corner			
	Mountain Gold Rush (S) Clinician top ranked	**Hot Air Balloon Race (MS)**	**Wheel of Chance (S)**	**Funnel Cake Falls (MT)**
Game description	Player rides rollercoaster along track and holds hands out to catch gold coins whilst avoiding red stars	Player steers hot air balloon along a course by moving both arms, avoiding the obstacles	Spin the wheel, (costs tickets to play) aim to win more tickets by spinning.	Player catches falling cakes on their plate, moving left and right to catch and balancing cakes as they fall
Age	Any (though younger target)	Any (though younger target)	Any (though younger target)	Any (though younger target)
Flexible entry	No	No	No	No
Game Start	Player raises left arm	Player raises left arm. Then moves both upper limbs to initiate balloon	Player raises left arm. Then moves both upper limbs to spin wheel	Player raises left arm.
Player/Game driven	Game Driven: Rollercoaster moves regardless of player	Player Driven: Player moves arms to initiate balloon movement	Player Driven: Player moves arms to initiate balloon movement	Game Driven: Cakes start to fall regardless of player
Stability	Yes: Standing	Yes: Standing	Yes: Standing	Yes: Standing
Mobility	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk
Agility	No	No	No	Yes: Side stepping
Spatial Accuracy	Yes: To reach for coins	No	No	Yes: to catch cakes
Game Duration	Consistent	Skill dependent: shortens	Skill dependent: gamble	Consistent
Cognitive operations	Response selection Planning Switching attention	Planning	Planning Response selection	Planning
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Not within game	Not within game	Not within game	Yes: Cakes fall at increased speed
Performance Indicator	Number of gold coins collected. Collect tickets	Position in race. Collect tickets for overall performance.	Collect tickets for dependent on skill/gamble	Number of cakes caught. Collect tickets for overall performance.

	for overall performance.			
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments			*Not specifically a game a way to spend tickets*	

	Carnival Games in Action – Launchpad Lane			
	Rocket to Moon (MT)	**Crash Test Dummy (MT)**	**Alley Ball (MT)**	**Pop Darts (MT)**
Game description	Player steers rocket using upper limbs to the moon, need to avoid colliding into obstacles.	Player uses their body to cover as many gold bricks as they can with your 'shadow on the wall' – Player needs to move and copy the position of the bricks	Player reaches for the ball then rolls it up the ramp aiming to score in the holes	Player reaches out to grab the darts then aims and throws the darts to pop the balloons
Age	Any (though younger target)	Any (though younger target)	Any (though younger target)	Any (though younger target)
Flexible entry	No	No	No	No
Game Start	Player raises left arm. Then uses both upper limbs to initiate steering rocket and jumps to start	Player raises left arm. Then game driven	Player raises left arm. Then move upper limb to initiate rolling ball.	Player raises left arm. Then moves upper limb to initiate throwing darts.
Player/Game driven	Player Driven: Player jumps to start	Game Driven: Shapes appear to player to copy regardless of player movement	Player Driven: Player moves arms to initiate rolling ball	Player Driven: Player moves arms to pick dart to throw
Stability	Yes: Standing	Yes: Standing	Yes: Standing OR SITTING	Yes: Standing OR SITTING
Mobility	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms (Legs) Trunk	Yes: Arms (Legs) Trunk
Agility	Yes: Jump to start then in standing	Yes: Includes squat/SLS/	No	No (Can side step to assist if played in standing but not essential)
Spatial Accuracy	Yes: To steer rocket	Yes: To match position	Yes: to aim roll of ball	Yes: To aim at balloons
Game Duration	Skill dependent: shortens	Consistent	Consistent	Consistent
Cognitive operations	Response selection Planning	Planning Response selection	Planning	Planning Response selection
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Not within game	Not within game	Not within game	Not within game

Performance Indicator	Speed/placing to reach moon. Collect tickets for overall performance.	Points scored. Collect tickets for overall performance.	Number of points scored/placing. Collect tickets for overall performance.	Number of balloons popped/total score. Collect tickets for overall performance.
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments		*Primary focus is matching position – target for proprioception/joint matching problems		

	Carnival Games in Action – Whirligig Way			
	Monkey See Monkey To (MT)	**Down the Stretch (MS)**	**Strength Test (MT)**	**Knockout Punch (MT)**
Game description	Player watches Monkey Barker dance, every time he stops dancing player needs to copy him with a 'mirror' image of his pose	Player uses flick of wrist to roll ball into the hole to move their horse down their track. Competing against other players in a race	Player has to raise hands above head and swing down to hit the target and move the bar as high as possible	Player is in a boxing ring environment, and uses arms to throw lefts, rights and ducks. Need to follow the sequence to progress to next round
Age	Any (though younger target)	Any (though younger target)	Any (though younger target)	Any (though younger target)
Flexible entry	No	No	No	No
Game Start	Player raises left arm. Then game driven	Player raises left arm. Then move upper limb to initiate rolling ball	Player raises left arm. Then move both upper limbs to raise hammer	Player raises left arm. Player moves upper limbs to initiate punching
Player/Game driven	Game Driven: Monkey moves regardless of player movement	Game Driven: Other horses race regardless of player participation	Player Driven: Player moves arms to swinging hammer	Player Driven: Player punches to begin sequence
Stability	Yes: Standing	Yes: Standing OR SITTING	Yes: Standing	Yes: Standing
Mobility	Yes: Arms Legs Trunk	Yes: Arms (Legs) Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk
Agility	Yes: Includes SLS	No	No	Yes: Includes ducking
Spatial Accuracy	Yes: To match position	Yes: To aim roll of ball	No	Yes: To punch at target/duck
Game Duration	Skill dependent: Lengthens	Consistent	Consistent	Skill dependent: lengthens
Cognitive operations	Response selection Planning	Planning	Planning Response selection	Planning Response selection
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Yes: Progress to next round within game	Not within game	Not within game	Not within game

Performance Indicator	Points scored/round progress to. Collect tickets for overall performance.	Points scored. Collect tickets for overall performance.	Round achieved/object progress to. Collect tickets for overall performance.	Points scored. Collect tickets for overall performance.
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments	*Primary focus is matching position – target for proprioception/joint matching problems			

	Carnival Games in Action – Tea Cup Court			
	Golden Arm (MT)	**Court King (MS)**	**Granny Shot (MT)**	**Hitting Streak (MT)**
Game description	Player is at fairground round aiming to throw ball to knock over the golden milk bottles. Trick is to aim throw to line up with the crosshairs	Player throws basketball overhead to shoot as many baskets as possible until the time runs out	Player has to get the object presented into the basketball hoop. Each object has a different weight therefore needs different amount of swing. Crouch low and swing ball high to shoot	Player is in a batting cage. Stand side ways and swing bat to hit the ball.
Age	Any (though younger target)	Any (though younger target)	Any (though younger target)	Any (though younger target)
Flexible entry	No	No	No	No
Game Start	Player raises left arm. Then move arm to reach for object.	Player raises left arm. Then move upper limbs to pick up ball.	Player raises left arm. Then move upper limb to pick up ball/object	Player raises left arm. Then game initiates pitching ball
Player/Game driven	Player Driven: Player drives game by picking up and throwing ball	Player Driven: Game responds to player throwing ball	Player Driven: Game responds to player throwing ball	Game Driven: Ball is pitched regardless of player action
Stability	Yes: Standing OR SITTING	Yes: Standing OR SITTING	Yes: Standing	Yes: Standing
Mobility	Yes: Arms (Legs) Trunk	Yes: Arms (Legs) Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk
Agility	No	No	Yes (squat to throw)	No
Spatial Accuracy	Yes: To throw at target	Yes: To aim shot into hoop	Yes: To aim underarm throw	YES: To swing bat at ball pitched at different speeds
Game Duration	Consistent	Skill dependent: Shortens	Consistent	Skill dependent: lengthens
Cognitive operations	Response selection Planning	Planning Response selection	Planning	Planning Response selection Switching attention
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Yes: Increase speed of	Not within game	Yes: Progress to next round and	Not within game

	movements to copy		increased weight of object	
Performance Indicator	Points scored. Collect tickets for overall performance.	Position in race. Collect tickets for overall performance.	Placing/category score. Collect tickets for overall performance.	Points scored. Collect tickets for overall performance.
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments				

	Kinect Sports					
	Soccer (MS) Participant top ranked	**Bowling (MS)**	**Beach Volleyball (MS)**	**Boxing (MS)**	**Table Tennis (MS)**	**Track and Field (MS)**
Game description	Player is in football match environment . Player passes and shoots by stepping and kicking, and then defends passes/acts as goalkeeper also	Player is in bowling venue. Bowls ball, playing against computer or other players	Player completing a game of beach volleyball. Player serves by using upper limb, and jumps for jump shot	Player is in boxing ring and competes in 3 rounds of boxing. Player punches high and low using upper limbs and blocks shot by covering face with arms	Player competing in table tennis match. Player serves using upper limbs and directs shots with trunk/arm positions	Player compete over five events. 1) Sprint (running on spot). 2) Javelin (runs on spot and release javelin with upper limb). 3) Long jump (run on spot and time jump). 4) Discus (time upper limb movement to release). 5) Hurdles (run on spot then time jump to clear hurdle)
Age	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)	Any (though target 8+)
Flexible entry	Yes (Beginner, Intermediate , Advanced)	Yes (Beginner, Intermediate , Advanced)	Yes (Beginner, Intermediat e, Advanced)	Yes (Beginner, Intermediat e, Advanced)	Yes (Beginner, Intermediat e, Advanced)	Yes (Beginner, Intermediate, Advanced)
Game Start	Player raises left arm. Then uses lower limb to pass to begin match	Player raises left arm. Then player picks up ball to bowl	Player raises left arm. Then play serves by moving arm to begin match	Player raises left arm. Then fight begins	Player raises arm. Then reaches to pick up paddle with arm and serves to begin	Player raises arm. Then event begins with sprint, race starts automatically.
Player/Gam e driven	Player Driven: Player needs to pass to initiate movement of ball	Player Driven: Player needs to pick up ball to bowl	Player Driven: Player needs to serve to begin game	Game Driven: Fight continues regardless of players involvemen t	Player Driven: Player needs to serve to continue with their own play	Mixed dependent on event. Races are game driven I.e. continue regardless of involvement. Field events are player driven
Stability	Yes: Standing	Yes: Standing	Yes: Standing	Yes: Standing (OR SITTING	Yes: Standing	Yes: Standing

				only if match has started)		
Mobility	Yes: Arms Legs Trunk Head	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk	Yes: Arms (Legs) Trunk	Yes: Arms Legs Trunk	Yes: Arms Legs Trunk
Agility	Yes: Side stepping	Yes: Side stepping	Yes: Side stepping and jumping	No	Yes: Side stepping	Yes: Running on spot and jumping
Spatial Accuracy	Yes: To direct pass/aim for goal	Yes: To aim ball	Yes: To direct serve/shot	Yes: To direct punch	Yes: To direct shot	Yes: To throw javelin/discus
Game Duration	Consistent	Consistent (fixed number of rounds)	Skill dependent: Shortens	Skill dependent: Shortens	Skill dependent: Shortens	Predominantly Consistent (same number of rounds for each field event. Races time dependent on performance)
Cognitive operations	Response selection Planning	Planning Response selection	Planning Response selection	Planning Response selection	Planning response selection	Planning Response selection Switching attention
Feedback	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Progression	Yes: Progress to performing different actions	Not within game	Not within game	Not within game	Not within game	Not within game
Performance Indicator	Game score. Can unlock achievements with overall performance	Score for game. Can unlock achievements with overall performance	Score/result of game. Can unlock achievements with overall performance	Win/lose contest. Can unlock achievements with overall performance	Score of game. Can unlock achievements with overall performance	Time/distance for each event, and points and position given for overall event. Can unlock achievements with overall performance
Instructions (visual or auditory)	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory	Visual and auditory
Additional Comments	Overall games typically longer than those on Kinect adventures/Carnival in action therefore suited to more able/older child					Bias on aerobic content. Most physically demanding game

Legend: MS (Multiplayer simultaneously), MT (Multiplayer turn taking), S (Single player)

Appendix 32 - Gaming matrix ASPECT WP4

X Box Game Choice Matrix

Agility	**Complexity/Length of Game** **Increasing demand** →		
Sitting/Static Stance SARA stance item ≤ 3 SARA gait item ≤3/4	Court King* (Carnival Games in Action – Tea Cup Court) Down the Stretch* (Carnival Games in Action – Whirligig Way) Hot Air Balloon Race (Carnival Games in Action – Coaster Corner)	Space Pop (Kinect Adventures) Mountain Gold Rush (Carnival Games in Action – Coaster Corner)	Boxing (Kinect Sports)
Dynamic Standing SARA stance item ≤ 2 SARA gait item ≤2/3	Funnel Cake Falls (Carnival Games in Action – Coaster Corner) Granny Shot (Carnival Games in Action – Tea Cup Court)	Rally Ball (Kinect Adventures) 20,000 Leaks (Kinect Adventures)	Soccer (Kinect Sports) Bowling (Kinect Sports) Table Tennis (Kinect Sports)
Propulsive Ability SARA stance item ≤1 SARA gait item ≤1/2	Rocket to the Moon (Carnival Games in Action – Launchpad Lane)	Reflex Ridge (Kinect Adventures) River Rush (Kinect Adventures)	Beach Volleyball (Kinect Sports)
Aerobic/Exercise Tolerance SARA stance item ≤1 SARA gait item ≤1			Track and Field (Kinect Sports)

* Can be played in sitting if participant requires break from standing games

- Kinect Adventures and Kinect Sports have beginner, intermediate and advanced options

- If participant has significant issue with proprioception can also choose
  - Crash Test Dummy (from Carnival Games in Action – Launchpad Lane)
  - Monkey See/Monkey To (from Carnival Games in Action – Whirligig Way)

Appendix 33 - Introductory letter ASPECT WP4

INSERT TRUST LOGO

Edge Hill University

Neurosciences Physiotherapy Team,
Physiotherapy Department,
Alder Hey Children's NHS Foundation Trust,
Eaton Road,
Liverpool
L12 2AP
0151 252 5660

INSERT DATE

Dear

ASPECT: A new study called "The ASsessment and Physiotherapy ManagEment of Children with ataxia following surgical resection of posterior fossa Tumour"

We are writing to let you know about a new research study that is being undertaken by my colleague Helen Hartley, a Specialist Paediatric Physiotherapist who is based at Alder Hey Children's Hospital. Helen is working with Alexandra Hollingworth Specialist Paediatric Physiotherapist at Royal Manchester Children's Hospital, alongside Edge Hill University for this research study.

The enclosed information sheet explains the aims and the details of this study. We would be very grateful if you could read this information.

If anything is unclear, or you have any questions about the study, please feel free to ring Helen Hartley on **0151 252 5660** or e-mail her at helen.hartley@alderhey.nhs.uk to discuss your queries. Or alternatively you can contact Ally Hollingworth on **0161 701 5438.**

Participation in the study is entirely voluntary and there is no obligation to take part. If however, you would like to participate either complete the enclosed reply slip and return it directly to Helen Hartley in the enclosed stamped envelope, or contact Helen by telephone or email.

Thank you for taking the time to consider contributing to this study.

Yours sincerely

Consultant Paediatric Oncologist

INSERT TRUST LOGO

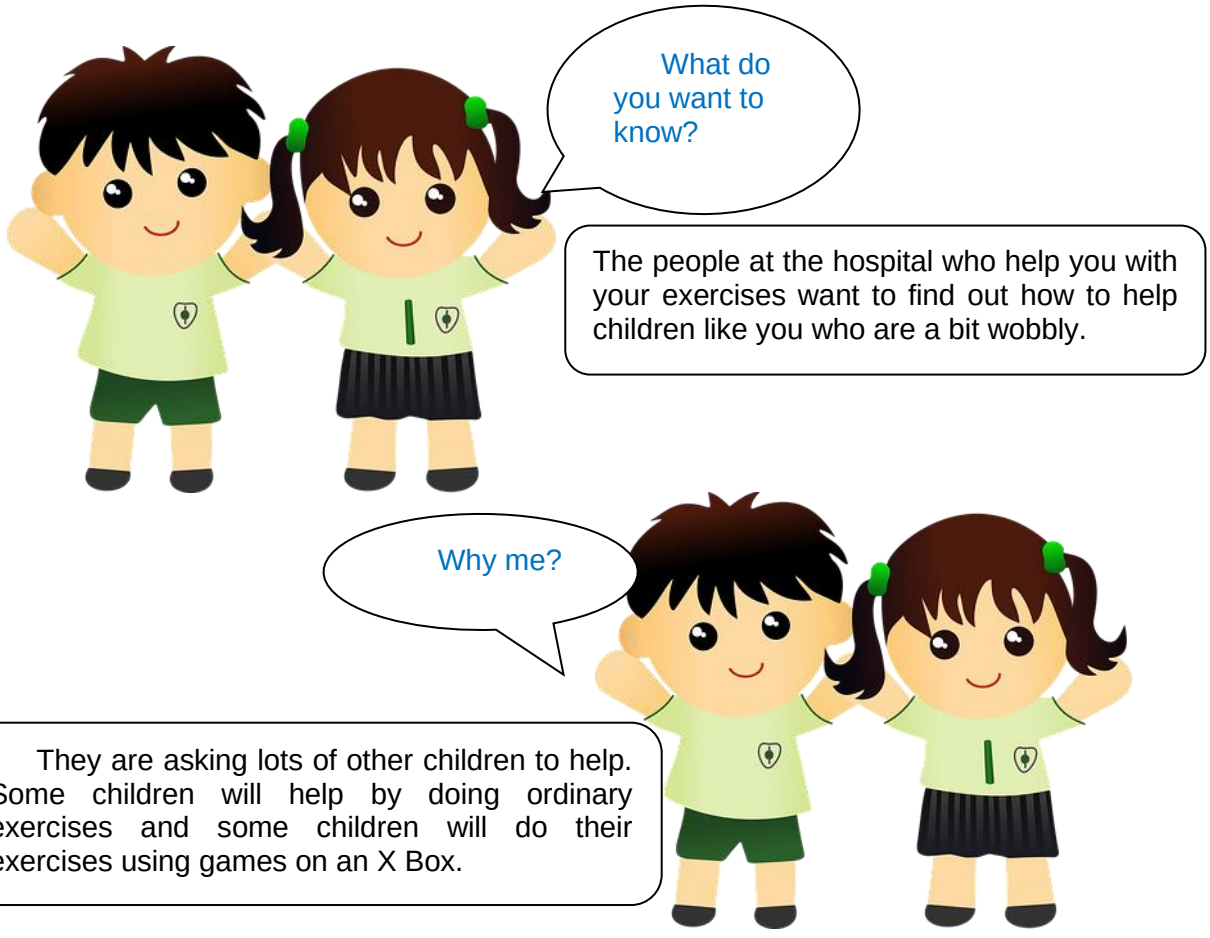
Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Information sheet to help parents explain to children 4-6 years of age (or children who may have difficulty reading the participant information leaflets)

The following prompts may be useful in explaining the study to your child



What do I have to do?

The way you can help them is by letting them look at the way you move your arms and legs and to see if you can stand up and walk around.

They will ask you to visit the hospital to do some physio/exercises and then to do them at home. Or you might just carry on with your normal physio/exercises at home.

They will check to find out if the exercises are helping you.

Who do I talk to?

If you are worried about anything then you can tell me about it and I will talk to the physios or the doctors or the people doing the project.

Do I have to take part?

If you do not want to be in the project you can tell me and I will talk to the people doing the project.

The people doing the project say thank you for your help.

Appendix 35 - PIS ASPECT WP4 Age 7-10 years

Are there any bad things about taking part?

We don't think there are any bad things about taking part.

Being part of the project will mean extra visits to the hospital.

Will anyone else know what I'm doing this?

Your mum/dad/carer will know that you are taking part and the physio who is helping you do your physiotherapy.

What if I have some questions?

If you have any questions about the study please talk to your parents/mum/dad/carer and they can contact INSERT PI NAME/DETAILS

Thank you for thinking about joining in this project.

INSERT TRUST LOGO

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Information Sheet for Children aged 7- 10 years

Introduction

Hello. My name is INSERT PI NAME.

I am asking you if you would like to take part in a project.

Before you decide if you want to take part, you need to know why I am doing the project and what will happen.

What is the project about?

This project is about physiotherapy for children like you who are a bit wobbly when they stand up or walk around.

Why have I been asked to take part?

We are asking children like you who have some problems with being a bit wobbly when you are walking to take part in this study.

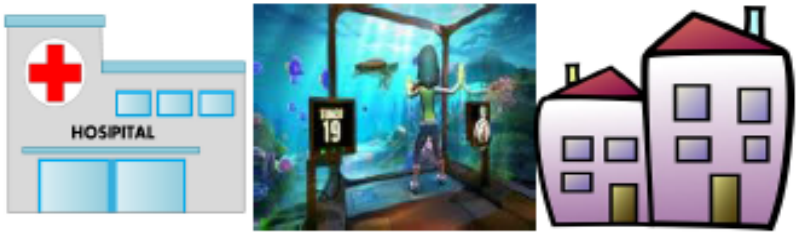
Your mum/dad/carer have said it is OK for you to take part if you want to.

Do I have to join in the study?

No! It is up to you whether you join in the study. If you decide to join in the study and then you change your mind, that is OK.

What will happen if I join in?

Some children will do their usual physiotherapy exercises and some children will do some extra exercises using an X Box Kinect.



Physio at the hospital using games like these then carry on at home

As part of the project your balance will be checked and a physio will ask you some questions about the exercises.

What are the good things about taking part?

We hope that you will enjoy taking part. We hope that this project might help us help other children.

Appendix 36 - PIS ASPECT WP4 Age 11-15 years

Will anyone else know that I'm doing this?

Your mum/dad/carer will know that you are taking part and the physio who is helping you do your physiotherapy. We will not tell anyone else and no-one will know what you have told us afterwards unless you tell us something which makes us think you are being harmed by someone. If we write anything up about the study, your name and other details will not be shared.

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more about this study. If new information becomes available during this study your physiotherapist will discuss it with you.

What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the INSERT PI DETAILS FOR SITE AND CI CONTACT

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk. You may also wish to contact the hospital complaints department on INSERT SITE CONTACT.

Many thanks for taking the time to read this information sheet

INSERT TRUST LOGO

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Information Sheet for Young People aged 11-15 years

Introduction

You are being invited to take part in a research study. Before you decide if you want to take part, you need to know why we are doing the project and what will happen. This information sheet tells you what the study is about.

What is the study about?

We would like to find out whether we can use X Box Kinect to support your physiotherapy and compare it with normal physio. This kind of study is called a feasibility trial. This means that we would also like to hear your views about taking part in the study to understand what went well and what didn't go so well. If you agree to take part in the study you will be put into one of two groups. One group will continue with their normal physio, the other group will also do extra physio using the X Box Kinect. You don't get to choose which group you will be in; a computer makes this decision.

Who is doing the study?

The main person doing the study is Helen Hartley. She is a physiotherapist who works at Alder Hey Children's Hospital. This study is part of the work she is doing at Edge Hill University for her PhD. She is working with other physiotherapists at INSERT SITE who will do your physiotherapy. Her study is being supervised by a team of researchers

Why have I been asked to take part?

You have had treatment for a posterior fossa tumour (in the back part of your brain) and you have some problems with balance/co-ordination. Your mum/dad/carer have said it is okay for you to take part if you want to.

Do I have to take part?

No! It is up to you whether you take part in the study. If you do take part, you can change your mind, without telling us why and no one will mind. Your decision will not affect your care.

What will happen if I take part?

A physiotherapist will assess your co-ordination (by asking to look at the way your arms and legs move) and ask you about day to day activities, and also check your balance. This will take about 30- 45 minutes and will be done during a visit to the hospital.

If you are in the X Box Kinect physio group, you will need to come to the hospital 3 times a week for your physio for the first four weeks. These will be extra visits unless you are already coming to the hospital for another appointment. After that, you will carry on with the X Box Kinect physio at home for another four weeks. As part of the study we will:

- ask you some questions about the X Box Kinect physio
- we will do the balance and co-ordination tests 3 times (this may involve extra visits if you are not already coming to the hospital for another appointment)
- ask you to write down in your study diary how much activity you do at home

If you are in the group doing your normal physio we will:

- ask you to come to the hospital for three extra visits so the physio can assess your balance and co-ordination
- ask you to write down in your study diary how much physiotherapy/activity you do during this time

Once you have finished your physio as part of this study we will ask what you and your parents thought about taking part.

What are the good things about taking part?

We hope that you will enjoy taking part. What we find out could help improve physiotherapy for other young people.

Are there any bad things about taking part?

We don't think there are any bad things about taking part. However, it will mean extra visits to the hospital. It will take up some of your time to talk to us after you have seen the doctor.

Appendix 37 - PIS ASPECT WP4 Age 16-18 years

INSERT TRUST LOGO

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Participant Information Sheet for Young People aged 16-18 years

Project Team

Helen Hartley – Paediatric Physiotherapist, Alder Hey Hospital
Prof Barry Pizer – Consultant Paediatric Oncologist, Alder Hey Hospital
Dr Ram Kumar – Consultant Paediatric Neurologist, Alder Hey Hospital
Prof Bernie Carter – Professor of Children's Nursing, Edge Hill University
Dr Lisa Bunn – Lecturer in Physiotherapy, Plymouth University
Dr Elizabeth Cassidy – Physiotherapist, Researcher

Principal Investigator for RMCH – Alexandra Hollingworth, Paediatric Physiotherapist

Introduction

Thank you for reading this information sheet. You are being invited to take part in a research study. Before you make your decision, it is important for you to understand why this study is being done and what it will involve. Please take your time to read the following information carefully. If anything is not clear to you or if you would like more information then please feel free to ask a member of the research team, whose details are at the end of this sheet. Please take time to decide whether or not you wish to take part.

Who is doing this research?

Therapists from the Neuro-physiotherapy team at Alder Hey Hospital with support from the Neuro-oncology team and the Physiotherapy Team at Royal Manchester Children's Hospital. The Chief Investigator is Helen Hartley, a Specialist Paediatric Physiotherapist. This study forms part of Helen's PhD studies which are funded by a NIHR (National Institute for Health Research) fellowship. The Principal Investigator for Royal Manchester Children's Hospital is Ally Hollingworth a Specialist Paediatric Physiotherapist.

What is the aim of the study?

The most common movement problem in children and young people with posterior fossa brain tumours is co-ordination and balance problems which are known as ataxia.

There are currently no guidelines on how much physiotherapy or which type is the best to complete for ataxia in children/young people following surgery for posterior fossa tumours.

This study aims to find out how practical it is to use virtual training e.g. X Box Kinect as part of physiotherapy. We are interested in whether using the X Box can help improve your balance and coordination when compared to usual physiotherapy, but before we can do that in a large scale study, we have to make sure that each part of the research project is practical and acceptable to children and young people. In order to do this we have to run a small scale version of a full study, and at each stage of the study find out which parts work well and where there might be some problems.

This study will compare the usual physiotherapy we do with young people to physiotherapy supported by using X Box Kinect games. We would like to measure how you respond to physiotherapy (for example the impact therapy might have on your balance, and day to day lives) at the start and the end of the study and we would also like to ask for your views about the therapy you receive in the study (X-box supported or usual physiotherapy)

Why have I been chosen?

Children aged up to the age of 18 who were diagnosed with a posterior fossa tumour 1-3 years ago (during the study period) and who have some balance/co-ordination problems may be eligible to take part.

We hope to recruit 20-25 children from Alder Hey and 20-25 children from Royal Manchester Children's Hospital to the study, over a 2 year period.

Do I have to take part?

No, it is entirely up to you to decide whether or not you take part. It will not affect your care whether you take part or not. You can change your mind at any point. You can take part in the study without completing the interview questions also if you don't want to. If you decide to stop taking part at any point, any information collected up to this point will be kept, however, nothing further will be collected.

What will happen if I decide to take part in the project?

Once you agree to take part in the study we will randomly allocate you into a study group. One group will continue with their normal physio/home exercises, the other group will also do additional physiotherapy using the X Box Kinect.
You don't get to choose which group you will be in – a computer program generates this at random. The assessor will not know what group you have been allocated to.

You will be assessed by a specialist physiotherapist specifically testing balance and co-ordination and we will ask you about day to day activities you may find difficult. This will take about 30- 45 minutes and will be done during a visit to the hospital. This will happen at the start of the study, 8 weeks into the study and at week 14 which is the end of the study.

If you are in the X Box Kinect physio group, you will need to come to the hospital 3 times a week for your X Box therapy for the first four weeks. (These will be extra visits if you don't have an existing hospital appointment we can link this with). Each session lasts about an hour. After that, you will carry on with the X Box Kinect therapy at home for another four weeks;
As part of the study we will:

- ask you some questions about the X Box Kinect therapy
- do the balance and co-ordination tests 3 times (at the start of the study, 8 weeks into the study and at week 14. This may involve extra visits if you are not already visiting the hospital)
- If you have any questions or want to progress the X Box Kinect physio programme an additional review by the physio at the hospital is available half way through the home training programme
- ask you to write down how much you have completed the X Box Kinect therapy at home in a study diary
- you should continue with any existing physiotherapy or activities you normally do during the study

We will loan you the X Box Kinect if you need this. It must be returned at the end of your 4 weeks of using it at home so another child/young person can use it.

If you are in the normal physio group we will:

- ask you to come to the hospital for three extra visits so the physio can assess your balance and co-ordination (when you enter the study, at 8 weeks and at week 14)
- ask you to write down in your study diary what physiotherapy/activities you have completed during the time you are in the study.

For both groups:
At the end of the study when you have completed all of their assessments we will ask for you and your parents views about taking part over the phone to gain further information. The interviews will be audio recorded with your permission. Some elements that you say may be quoted in the final report or any publications though these will be anonymised.

Please note the virtual training will not continue after the study has been completed.

Are there any benefits to me taking part?

We do not know if there will be any direct benefit for you. We hope that what we learn from this study may benefit other children and young people in the future.

Are there any disadvantages or risks involved in my participation in this study?

Apart from the extra visits to the hospital we do not think there are any disadvantages to you taking part in the study. We do not think that are any risks for you taking part in the X Box Kinect physio but the physios who help to do the X Box Kinect training in the hospital will advise you about how much to challenge yourself to keep safe when you are playing the games at home.

What will happen with the results of my assessments?

The assessments of your balance and co-ordination will be identified by a study code (anonymized) and analysed. If you would like to know the results of your assessments they will be available at the end of the study, just ask the research team.

What will happen to my information?

All information will be kept private, confidential and secure. Only people directly clinically involved in this study will be able to look at your records, although some sections of medical notes and data collected during the study may be looked at by individuals from regulatory authorities (such as the National Institute for Health Research) or from the NHS Trust (both monitor documentation/records to make sure studies are done properly). Your assessment results will be labeled with a non-identifiable code.
Once the study is complete all personal information will be securely stored (encrypted and password protected on a non-mobile device within the NHS Trust) for up to 6 months by the lead researcher (e.g. contact details). At 6 months all of the non-identifiable information will be kept for a total of 10 years in line with Alder Hey Children's NHS Foundation Trust procedures for handling, processing, storage and destruction of data and the Data Protection Act 1998.

How can I claim our expenses?

Costs related to additional visits can be reimbursed. Acceptable expenses include; standard class train/bus tickets, mileage at 40p per mile and car parking. Please provide information and receipts where possible to the research team.

What if new information becomes available?

If new information becomes available during this study your physiotherapist will discuss this with you.

What happens when the research study stops?

We plan to have finished the study in 2020 and have written all the reports by April 2021. If you would like, we will send you a short summary of the research study when it is finished, just let us know.

What will happen to the results of the research study?

The results of the study will be shared across the NHS and will inform future work. We plan to write articles and present the findings to help us share our ideas with other professionals. We hope it will help inform physiotherapy practice.

Who is funding this study?

The funding for the study is coming from the National Institute of Health Research who are funding Helen Hartley's Clinical Doctoral Fellowship (ICA-CDRF-2016-02-065). The other members of the research team will not receive any personal payments for undertaking this research.

Who has reviewed the study?

The study has been reviewed by the Faculty of Health and Social Care Research Ethics Committee at Edge Hill University and by the National Research Ethics Service (committee details and numbers to be added).

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain, or have concerns about any aspect of the way you have been treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more.

If you have any concerns or other questions about this study or the way it has been carried out, you should contact INSERT PI DETAILS FOR SITE or you can contact the Chief Investigator (Helen Hartley

0151 252 5236) or you can contact Helen's Director of Studies, Professor Bernie Carter via email bernie.carter@edgehill.ac.uk or phone 01695 657771

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk.

You may also wish to contact the hospital complaints department on INSERT TRUST SPECIFIC CONTACT.

Many thanks for taking the time to read this information sheet

Appendix 38 - PIS ASPECT Parent information sheet

INSERT TRUST LOGO

Edge Hill University

The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Information Sheet for Parents

Project Team

Helen Hartley – Paediatric Physiotherapist, Alder Hey Hospital
Prof Barry Pizer – Consultant Paediatric Oncologist, Alder Hey Hospital
Dr Ram Kumar – Consultant Paediatric Neurologist, Alder Hey Hospital
Prof Bernie Carter – Professor of Children's Nursing, Edge Hill University
Dr Lisa Bunn – Lecturer in Physiotherapy, Plymouth University
Dr Elizabeth Cassidy – Physiotherapist, Researcher

Principal Investigator for RMCH – Alexandra Hollingworth, Paediatric Physiotherapist

Introduction

Thank you for reading this information sheet. You and your child are being invited to take part in a research study. Before you make your decision, it is important for you to understand why this study is being done and what it will involve. Please take your time to read the following information carefully. If anything is not clear to you or if you would like more information then please feel free to ask a member of the research team, whose details are at the end of this sheet. Please take time to decide whether or not you wish to take part.

Who is doing this research?

Therapists from the Neuro-physiotherapy team at Alder Hey Hospital with support from the Neuro-oncology team and the Physiotherapy team at Royal Manchester Children's Hospital. The Chief Investigator is Helen Hartley, a Specialist Paediatric Physiotherapist. This study forms part of Helen's PhD studies which are funded by a NIHR (National Institute for Health Research) fellowship. The Principal Investigator for Royal Manchester Children's Hospital is Ally Hollingworth Specialist Paediatric Physiotherapist.

What is the aim of the study?

There are currently no guidelines on how much physiotherapy or which type is best for ataxia (balance and movement difficulties) in children/young people following surgery for posterior fossa tumours.

This study aims to find out how feasible it is to use virtual training e.g. X Box Kinect as part of physiotherapy. We are interested in whether virtual training can help improve children's balance and coordination problems when compared to usual physiotherapy, but before we can do that in a large scale study, we have to make sure that each part of the research project is practical and acceptable to parents and children. In order to do this we have to run a small scale version of a full study, and at each stage of the study find out which parts work well and where there might be some problems

This study will compare the usual physiotherapy we do with children to physiotherapy supported by using X Box Kinect games. We would like to measure how your child responds to physiotherapy (for example the impact therapy might have on their balance, and day to day lives) at the start and the end of the study and we would also like to ask for your views and your child's views about the therapy they receive in the study (X-box supported or usual physiotherapy)

Why have I and my child been chosen?

Children aged up to the age of 18 who were diagnosed with a posterior fossa tumour 1-3 years ago (during the study period) and who have some balance/co-ordination problems may be eligible to take part.

We hope to recruit 20-25 children from Alder Hey and 20-25 children from Royal Manchester Children's Hospital to the study, over a 2 year period.

Do I have to take part and what about my child?

No, it is entirely up to you to decide whether or not you and/or your child takes part. It will not affect your child's care whether you take part or not. You can stop at any point. If you decide to stop taking part at any point, any information collected up to this point will be kept, however, nothing further will be collected.

What will happen if I and/or my child decide to take part in the project?

Once you and your child agree to take part in the study we will randomly allocate your child into a study group. One group will continue with their normal physio/home exercises, the other group will also do additional physiotherapy using the X Box Kinect.
You don't get to choose which group your child will be in – a computer program generates this at random. The assessor will not know what group your child has been allocated to.

Your child will be assessed by a specialist physiotherapist specifically testing balance and co-ordination and we will ask you/your child about day to day activities they may find difficult. This will take about 30- 45 minutes and will be done during a visit to the hospital. This will happen at the start of the study, 8 weeks into the study and at week 14 which is the end of the study.

If your child is in the X Box Kinect physio group, you will need to bring them to the hospital 3 times a week for X-box therapy for the first four weeks. (These will be extra visits if your child doesn't have an existing hospital appointment we can link this with). Each therapy session lasts about an hour. After that, they will carry on with the X Box Kinect physio at home for another four weeks; they might need your support to do this.
As part of the study we will:

- ask you and your child (if they are old enough and agree) some questions about the X Box Kinect physio (this will take place at the end of week 1 and end of week 4 and will be audio recorded with your permission)
- do the balance and co-ordination tests 3 times (at the start of the study, 8 weeks into the study and at week 14. This may involve extra visits if your child is not already visiting the hospital)
- If you have any questions or want to progress the X Box Kinect physio programme an additional review by the physio at the hospital is available half way through the home training programme
- ask you and your child to write down how much they have completed the X Box Kinect physio at home in a study diary
- Your child should continue with his or her usual physiotherapy treatment during the study

We will loan you the X Box Kinect if you need this. It must be returned at the end of your 4 weeks of using it at home so another child/young person can use it.

If your child is in the normal physio group we will:

- ask you to bring them to the hospital for three extra visits so the physio can assess their balance and co-ordination (when your child enters the study, at 8 weeks and at week 14)
- talk to you and your child about the exercises you do.

- ask you/your child to write down in a diary when your child has completed physio or exercises during the time they are in the study

For both groups:
At the end of the study when your child has completed all of their assessments we will ask for your views about taking part over the phone to gain further information. Your child can help with this too if they would like to. This will be a short interview lasting 10-15 minutes. This interview will be audio recorded with your permission.

Please note the virtual training will not continue after the study has been completed.

Are there any benefits to me and my child taking part?

We do not know if there will be any direct benefit for your child. We hope that what we learn from this study may benefit other children in the future.

Are there any disadvantages or risks involved in my child's participation in this study?

Apart from the extra visits to the hospital we do not think there are any disadvantages to your child and you taking part in the study. We do not think that are any risks for your child taking part in the X Box Kinect physio but the physios who help to do the X Box Kinect training in the hospital will advise you and your child about how much to challenge themselves to keep them safe when they are playing the games at home.

What will happen with the results of my child's assessments?

The assessments of your child's balance and co-ordination will be identified by a study code (anonymised) and analysed. If you would like to know the results of your child's assessments they will be available at the end of the study, just ask the research team.

What will happen to my child's information?

All information will be kept private, confidential and secure. Only people directly clinically involved in this study will be able to look at your child's records, although some sections of medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust (both monitor documentation/records to make sure studies are done properly). Your child's assessment results will be labeled with a non-identifiable code.

What will happen to the information I provide?

The interviews will be audio recorded with your permission. Some elements that you say may be quoted in the final report or any publications though these will be anonymised. Data stripped of any personally identifying details collected during the study, including that from interviews may be looked at by individuals from regulatory authorities (such as the National Institute of Health Research) or from the NHS Trust. Your child can take part in the study even if you do not want to take part in the interviews, just let us know. Once the study is complete all personal information will be securely stored (encrypted and password protected on a non-mobile device within the NHS Trust) for up to 6 months by the lead researcher (e.g. contact details). At 6 months all of the non-identifiable

information will be kept for a total of 10 years in line with Alder Hey Children's NHS Foundation Trust procedures for handling, processing, storage and destruction of data and the Data Protection Act 1998.

How can I claim our expenses?

Costs related to additional visits can be reimbursed. Acceptable expenses include; standard class train/bus tickets, mileage at 40p per mile and car parking. Please provide information and receipts where possible to the research team.

What if new information becomes available?

If new information becomes available during this study your physiotherapist will discuss this with you and your child.

What happens when the research study stops?

We plan to have finished the study in 2020 and have written all the reports by April 2021. If you would like, we will send you a short summary of the research study when it is finished, just let us know.

What will happen to the results of the research study?

The results of the study will be shared across the NHS and will inform future work. We plan to write articles and present the findings to help us share our ideas with other professionals. We hope it will help inform physiotherapy practice.

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The funding for the study is coming from the National Institute of Health Research who are funding Helen Hartley's Clinical Doctoral Fellowship (ICA-CDRF-2016-02-065). The other members of the research team will not receive any personal payments for undertaking this research.

Who has reviewed the study?

The study has been reviewed by the Faculty of Health and Social Care Research Ethics Committee at Edge Hill University and by the National Research Ethics Service (committee details and numbers to be added).

What if something goes wrong?

If your child is harmed by taking part in this research project, there are no special compensation arrangements. If your child is harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain, or have concerns about any aspect of the way you have been treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

Who can I contact if I want to take part or want more information?

The physiotherapist who gave you this information leaflet can tell you more.

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the INSERT PI DETAILS FOR SITE or you can contact the Chief Investigator (Helen Hartley 0151 252 5236) or you can contact Helen's Director of Studies, Professor Bernie Carter via email bernie.carter@edgehill.ac.uk or phone 01695 657771

If you wish to speak to someone independent and who is based at Edge Hill University, please contact Professor Clare Austin, Associate Director, Research & Innovation on 01695 650772 or email austincl@edgehill.ac.uk.
You may also wish to contact the hospital complaints department on INSERT SITE CONTACT NUMBER.

Many thanks for taking the time to read this information sheet

Appendix 39 - Assent ASPECT WP4

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Edge Hill University

Child Assent Form: The ASPECT Study

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: INSERT PI DETAILS

		Please initial box
1.	I have read the information about the study or had it read to me	
2.	I understand what the study is about and have asked all the questions I want to	
3.	I understand that I do not have to take part and can stop at any time	
4.	I know that the interview I take part in will be recorded. I understand I can say whether or not I am happy to be recorded I know that some of the things I say might go into the report but that no one will know it was me that said it	
5.	I understand that parts of any of my medical notes may be looked at by responsible people who have special permission to do this. I am happy for these people to look at my records.	
6.	I agree to take part in the above study and any interviews required	
7.	I agree to take part in the above study but do not want to complete the interviews	

Name of Child	Date	Signature
Name of Person verifying assent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 40 - Consent 16+ ASPECT WP4

INSERT TRUST LOGO

Edge Hill University

Young Person (aged 16-18 years) Consent Form
The ASPECT Study

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: INSERT PI DETAILS

		Please initial box
1.	I confirm that I have read and understand the information sheet dated (version) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that the interviews with me will be audio-recorded with my permission and that some of the things I say may be quoted in the final report or any publications and I understand that these will be anonymised.	☐
4.	I understand that sections of my medical notes and/or data collected during the study may be looked at by responsible individuals involved in the research or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
5.	I agree to take part in the above study and any required interviews.	☐
6.	I agree to take part in the above study but do not want to complete any interviews	☐

Name of Young Person	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 41 - Parent consent for child ASPECT WP4

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Edge Hill University

Parent/Carer Consent Form for their child to participate: The ASPECT Study

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: INSERT PI DETAILS

		Please initial box
1.	I confirm that I have read and understand the information sheet dated (version) for the above study and have had the opportunity to ask questions.	
2.	I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	
3.	I understand that the interviews with my child will be audio-recorded with their permission. I understand that some of the things they say may be quoted in the final report or any publications and I understand that these will be anonymised.	
4.	I understand that sections of my child's medical notes and/or the data collected during the study may be looked at by responsible individuals involved in the research or from regulatory authorities where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records.	
5.	I agree for my child to take part in the above study including any interviews	
6.	I agree for my child to take part in the above study but do not want them to participate in any interviews	

Name of Parent consenting on child's behalf	Date	Signature
Name of Child	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 42 - Parent consent ASPECT WP4

INSERT TRUST LOGO

Edge Hill University

Parent/Carer Consent Form: The ASPECT Study

Study Number:
Patient Identification Number for this trial:

Title of Project: ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour (ASPECT)

Name of Researcher: INSERT PI DETAILS

		Please initial box
1.	I confirm that I have read and understand the information sheet dated (version) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected.	☐
3.	I understand that the interviews with me will be audio-recorded with my permission and that some of the things I say may be quoted in the final report or any publications and I understand that these will be anonymised.	☐
4.	I understand that the data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust. I give my permission for these individuals to have access to the records.	☐
5.	I agree to take part in the above study.	☐

Name of Participant (Parent)	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 43 - Baseline data ASPECT WP4

ASPECT STUDY - BASELINE INFORMATION SHEET

Patient Identification Number for this trial: _____

Age at diagnosis _____

Age at time of entering trial _____

Diagnosis (include tumour location/histology/molecular subtype)

_____
_____
_____

Treatment Received (surgery, chemotherapy, radiotherapy)

_____
_____
_____

Current medication

_____
_____

Co-Morbidities -

_____
_____

Currently receiving physiotherapy? _____

If Yes, detail frequency, type, setting (e.g. seen x1 weekly in school for balance exercises)

_____
_____
_____

Currently has home exercise programme? _____
If Yes, detail nature and how often completes

_____
_____

Does any other physical activity? _____
If Yes, detail frequency, type, setting

_____
_____

Appendix 44 - Rater Protocol ASPECT WP4

ASPECT STUDY – ASSESSOR PROTOCOL

- Introduce self to child and family/carers
- Complete each outcome measure in full before moving onto the next outcome measure
- Ensure adequate space for assessing prior to commencement of the outcome measures

- When completing the SARA;
  - The child should be barefoot
  - Use the instructions at the beginning of each item (language can be adapted for differing age groups)
  - Visual prompts can be used if required
  - The items can be completed in any order
  - Record each score on the SARA sheet
  - Record the time it takes to complete all items

- When completing the BARS;
  - The items can be completed in any order
  - The gait item is completed over a 10m distance (pre marked before the start of the test)
  - Visual prompts can be used if required
  - Record each score on the BARS sheet
  - Record the time it takes to complete all items

- When completing the PEDI;
  - complete the mobility and self care domain of the PEDI
  - items should be scored as 0 (unable) or 1 (capable)
  - capable refers to what child can do without help
  - can score 1 for skills that have mastered earlier and progressed beyond but if have lost skills credit only current capabilities
  - if 2 components of task are listed with an AND statement must be able to do both parts
  - the PEDI can be completed by professional judgment of the therapist or by parent report (or a combination, note items answered by parent)
  - complete the PEDI in conjunction with the manual
  - add the scores at the end (raw score out of 59)
  - and complete the caregiver section that links with the mobility and self-care domain
  - record the time it takes to complete all items

- When completing the 9 HPT
  - Use instruction as directed with the scoring sheet
  - Ensure stop watch is calibrated prior to commencement
  - Record scores on 9HPT scoring sheet

- When completing the PBS
  - Use instruction as directed with the scoring sheet
  - Ensure have appropriate equipment ready (step, pencil, ruler)
  - Record scores on PBS scoring sheet
  - Record the time it takes to complete all items

- When completing the PedsQL

    - Select appropriate questions for child's age
    - Parental version is sufficient for completion
    - Record on Peds QL sheet
    -
- When completing the INAS
    - Follow specific information according to INAS instructions
    - Refer to notes re eye movement section as required
    - Complete INAS form

- When completing the subjective scale
    - Ask parents for their impression to complete on individual form

- Record your global clinical impression of ataxia (no, mild, moderate or severe at the end of completing the other outcome measures)

- Any items that are not able to be tested record as NT
- Transfer all scores and times to the data collection sheet
- Give the data collection sheet to the research administrator immediately at the end of the assessment
- Do not discuss the results of the outcome measures with the other therapists

Appendix 45 - Intervention Log ASPECT WP4

ASPECT STUDY - Intervention Record Sheet

Participant Identification Number _____ Therapist ID _____ Date _____

Any new concerns/medical issues

_____

_____

Video Game Used	Sub Game Played	Position played in	Time Spent Playing	Level played if appropriate (e.g. beginner)	Score achieved/points recorded	Comments (INCLUDE REASON FOR PROGRESSION IF APPROPRIATE)

Any additional comments

_____

_____

If the child/parent/guardian wish to withdraw from the study and give a reason for this please record _____

_____

Please store this sheet as per study guidelines

Appendix 46 - Postcard ASPECT WP4

Just a reminder to fill in your study diary!

If you have any questions please contact the study team.Helen Hartley 0151 252 5660 or helen.hartley@alderhey.nhs.uk

Appendix 47 - Training plan ASPECT WP4

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The ASPECT Study – Training Booklet

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Participant Number:

Welcome! Thank you once again for volunteering for this study. This booklet explains the X Box therapy we would like you to do three times a week. The activities will have been explained and shown to you by a member of the research team. If you have any questions please contact us on:

Helen Hartley 0151 252 5660 helen.hartley@alderhey.nhs.uk or Ally Hollingworth 0161 701 5438

ASPECT WP4 Generic Training Plan Version 1.0 11.08.2017

Your Customised Training Plan

This section outlines the X Box activities we would like you to do. It will be filled out after discussion with a research physiotherapist and after you have tried the games.

Game	Initial level	Target Time	Progression	Notes

Appendix 48 - Participant diary ASPECT WP4

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The ASPECT Study

The ASsessment and Physiotherapy managEment of ataxia in Children following surgical resection of posterior fossa Tumour

Participant Daily Diary

Participant Number

ASPECT WP4 Generic Participant Diary Version 1.0 11.08.2017

Welcome!

Thank you once again for volunteering for this study. As part of the study we would like you (or your parent) to complete this diary every day.

Every day we would like you to write down what treatment or activities you have done, how long you did them for and then some comments. This could include any X Box therapy we ask you to do if you are in the intervention group, but also other treatments/activities such as;

- Your normal physiotherapy sessions (please tell us briefly what type of exercises you did in physio e.g. balance exercises, activities in kneeling/on your hands and knees)
- Exercises you may do at home by yourself/with your family e.g. stretches or strengthening exercises
- Any sports activities you may have taken part in at school or with a club or with your friends (e.g. football, rugby). (You can use the stickers to help if you would like to show us which sports you did)
- Going for a walk or swim

Day	Treatments Activity	Duration	Comments
1 Tuesday 1st August	Went swimming with dad Stretching exercises with mum	About half an hour 15 minutes	Did lots of splashing – it was fun My legs felt tight
Other Comments	We were on holiday this week.		

It is important to be as honest and accurate as you can but don't worry if you cannot exercise every day.

You will receive a postcard after 2 weeks to remind you to fill in this diary, then a member of the research team will ring you after 5 weeks to check that you are getting on ok.

In the meantime if you have any questions or problems please contact: **Helen Hartley 0151 252 5660 helen.hartley@alderhey.nhs.uk**

ASPECT WP4 Generic Participant Diary Version 1.0 11.08.2017

Week 1

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 2

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 3

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 4

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 5

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 6

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 7

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Week 8

Day	Treatments/ Activity	Duration	Comments
1			
2			
3			
4			
5			
6			
7			

Other comments

Thank you for taking the time to complete this diary!

Please remember to bring it with you to your assessment session at the end of the study.

Appendix 49 - Subjective impact ASPECT WP4

Name/Patient ID _____ Rater _____ Date _____

Subjective Impact – Likert Scale ASPECT Study

PATIENT/FAMILY/CARER GLOBAL IMPRESSION OF CHANGE

How has your/your child's ataxia/co-ordination changed since their last assessment?

Much better ☐

Minimally better ☐

No change ☐

Minimally worse ☐

Much worse ☐

If not done please record (and reason)

_____

Appendix 50 - Embedded qualitative interviews ASPECT WP4

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Embedded Qualitative Interview Questions and Prompts (Week 1 and Week 4 of intervention)

Participant ID :

Time: **Date:** **Location:**

Participant's verbal consent to audio recording: YES/NO

Reminder that this interview will be audio recorded to allow me to remember what we said. Any answers and direct quotes used in any publication or presentation will not use your name and no one will know that it was you

Semi-structured interview form

Please note Child's views can be supported by the completion of the chosen app if preferred

Participants questions

Week 1 interview about hospital based sessions	**Week 4 interview about hospital based sessions**
1. How did you like X Box training this week? How it has been?	1. How has the X box training been this week?
2. Was it what you expected?	2. What word would you use to describe this week's training? [boring, ok, or fun – keep these as prompts, but try to elicit the perspectives of the participant first]
3. Did anything surprise you about the training?	3. Thinking about the whole week, what has been easy? (too easy?)
4. What word would you use to describe this week's training? [boring, ok, or fun – keep these as prompts, but try to elicit the perspectives of the participant first]	4. Again, thinking about the whole week, has anything been difficult? (too difficult?)
5. Thinking about the whole week, what has been easy? (too easy?)	5. Which games have you enjoyed the most/had most fun with?
6. Again, thinking about the whole week, has anything been difficult? (too difficult?)	6. Which games have you had least fun with/enjoyed the least?
7. Which games have you enjoyed the most/had most fun with?	7. Is there anything you don't like about X box training?
8. Which games have you had least fun with/enjoyed the least?	8. Did you mind coming to the hospital for the training sessions?
9. Is there anything you don't like about X box training?	9. Is there anything else you'd like to tell me about this training programme?
10. Do you have any questions about the exercise diary?	
11. Is there anything else you'd like to tell me about this training programme so far?	

Parent(s) questions;

Week 1 interview about hospital based sessions	**Week 4 interview about hospital based sessions**
Thinking about this week's sessions;	Thinking about this week's sessions;
1. Do you think the length of sessions are ok?	1. Do you think the length of the sessions are ok?
2. Was three times a week this week about right or too little or too much?	2. Was three times a week ok this week (about right, too little, too much)?
3. Have you had any problems attending the sessions (timing, parking/transport, other appointments (self or child), fitting appointments around work/school/other activities)	3. Since we last talked about this, have you had any problems attending the sessions (timing, parking/transport, other appointments (self or child), fitting appointments around work/school/other activities)
4. Has your child had any problems while doing the training this week? (fatigue, sore, stiff, any other changes that you're worried about?)	4. Has your child had any problems while doing the training this week/in the last 3 weeks? (fatigue, sore, stiff, any other changes that you're worried about?)
5. Do you think X box training is sufficiently challenging (too easy/too difficult)?	5. Do you think X box training is sufficiently challenging this week (too easy/too difficult)?
6. Is there anything else you'd like to say about the training programme so far?	6. Is there anything else you'd like to say about the training programme so far?

Signed:
Dated:

Appendix 51 - Exit interview ASPECT WP4

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Edge Hill University

Exit Interview Questions and Prompts

Participant ID :
Time: **Date:** **Location:**

Participant's verbal consent to audio recording: YES/NO
Reminder that this interview will be audio recorded to allow me to remember what we said. Any answers and direct quotes used in any publication or presentation will not use your name and no one will know that it was you.

Overall participation questions
In your own words what was it like being part of the ASPECT trial?

Prompts:

- Can you tell me what you liked? What you disliked? What was easy? What were the challenges?
- Can you comment on the time commitment required from you and your child for this study? (Were the assessments too long/too short? Was it ok filling in the diary every day?)
- Is there anything you would change? How could we improve it? How easy/difficult was it to fit into you and your child's normal routine of school?
- What were your reasons for taking part?
- Did you ever think of stopping being part of the trial? If so why, and what made you decide to keep going?

Overall participation questions for participants who did not complete the study
In your own words what was it like being in the ASPECT trial?

- Can you tell me what you liked? What you disliked? What was easy? What were the challenges?
- Can you comment on the time commitment required from you and your child for this study? (Were the assessments too long/too short? Was it ok filling in the diary every day?)
- Is there anything you would change? How could we improve it? How easy/difficult was it to fit into you and your child's normal routine of school?
- What were your reasons for taking part?
- What made it difficult for you to complete the study?
- Is there anything that would have helped you to continue in the study?

Virtual Training (if in the intervention group)
In your own words can you tell me about your experience of taking part in the virtual training as part of this study?

Prompts:

- How did the virtual training compare to anything you/your child has done before? How did you find the specific games? Is there anything you would change? Were the games too easy

or too difficult for you? Explain Was there anything in particular you liked about it? What part did you enjoy the most?

- Anything you particularly disliked about it? Which games did you like the least? Can you tell me why/what about it you liked/disliked?
- Did you/your child have any problems/adverse effects (incidents) while doing the virtual training?
- Would you have preferred longer/shorter sessions, spread over more weeks/fewer weeks, more sessions per week/fewer?
- Home based element; How did the home virtual training programme compare to anything you've done before? How did you find the virtual training programme that was set for you/your child? Is there anything you would change? Were the exercises too easy or too difficult for you? Were there any problems with doing the virtual training at home? Explain
- Do you think doing the virtual training has helped you/your child?
- How did the study impact on everyday life for (a) the family and (b) your child (thinking about school, friendships, tiredness and fatigue etc)?
- On balance, would you undertake the home virtual training programme again?
- Did you find it easy to complete the study diary? (What would have helped to make it easier?)
- Refer to participants diary if indicated to clarify any issues

Usual Care Group

- How did you find attending for assessments although you weren't in the intervention group?
- Did you do anything differently in the time frame you were in the study e.g. more physio/different activities at home
- Did you find it easy to complete the study diary? (What would have helped to make it easier?)
- Refer to participants diary if indicated to clarify any issues

Previous Physio Experience VS ASPECT Study

Before taking part in the ASPECT trial what sort of exercises/activities did you/your child do? Are you doing exercises or attending Physio outside of the ASPECT study at the moment?

Prompts

- How often, amount of time, home exercise programme, type of exercises.

Other

- Any other comments about any element of the study?
- What would be your main piece of advice for someone running a physiotherapy study like this? In your opinion, what have been the main benefits and disadvantages of taking part in this study?

General Prompts and Probes

How did that make you feel?
That's interesting can you tell me more about that?
Can you elaborate a little more?
Could you clarify that?
I am not quite sure I understand. You were saying?
When you say …….. Did you mean that……..

Signed: **Dated:**

Appendix 52 – Data Management Plan

ASPECT Study – Data Management Plan

ADMIN DETAILS

Project Name: ASPECT – The ASsessment and Physiotherapy management of ataxia in Children following surgical resection of posterior fossa Tumour

Principal Investigator / Researcher: Helen Hartley

Institution: Edge Hill University

DATA COLLECTION

What data will you collect or create?

This project will generate different types of raw data from the individual work packages.

WP1 – Quantitative data collected from a number of physiotherapy/mobility-based outcome measures. This will be collated into spreadsheets.

WP2 – Predominantly qualitative data collected from responses to an e-survey from physiotherapists.

WP3 – Qualitative date collected from participants (children and parents and clinicians) during 3 workshops in the form of postcards/proformas.

WP4 – Mixed quantitative and qualitative data collected during feasibility RCT (will include interview responses, study diaries and results of outcome measures which will be collated into spreadsheets)

How will the data be collected or created?

WP1 – Data has been collected by assessing children with ataxia using a number of outcome measures including ataxia scales and functional mobility measures.

WP2 – Data will be collected through the administration of an e survey targeted at clinicians working with children with ataxia following surgical resection of posterior fossa tumour.

WP3 – Data will be collected through a series of workshops with involvement from children and their families and clinicians. This will include postcards/notes/proformas.

WP4 – Quantitative data will be collected through the completion of a feasibility RCT and will include aspects such as process measures and there will also be secondary quantitative data through the collection of scores of outcome measures. Qualitative data will be collected through a series of semi structured interviews from 50% of the intervention group. Interviews will be recorded with the participants permission and then transcribed.

DOCUMENTATION AND METADATA

What documentation and metadata will accompany the data?

WP1 – Individual outcome measure results are recorded on appropriate scoring sheets and there is a baseline data collection sheet al.so for overall scores. Case report forms (CRF) are completed for each patient and held in the site specific file at the sponsor site. The master site file held in the Oncology Research Team contains the screening log and original consent forms.

WP2 – Data will be exported from Survey Monkey (to a password protected file held on secure network computer at the sponsor site) and evaluated to inform the protocol for WP4.

WP3 – Notes/proformas and postcards generated by discussion at the workshops will be pseudo-anonymised and used for the purpose of refining the protocol for WP4.

WP4 –Individual outcome measure scoring sheets will be used with overall scores recorded on baseline data collection sheets. This will be pseudo-anonymised with participants allocated a code. These will be retained at each site (CRFs will be completed for all participants and held in the main site file at the sponsor site). Scores from the outcome measures will be transferred from the CRFs onto an electronic spreadsheet. With respect to the qualitative data generated by the semi structured interviews, the interviews will be audio-recorded and the recordings will be typed up by the researcher and then the audio-recordings deleted. The interview transcripts will be pseudo-anonymised.

ETHICS AND LEGAL COMPLIANCE

How will you manage any ethical issues?

WP1 – Ethics approval is already in place following previous application through the IRAS system REC ref 12/NW/0169, IRAS project ID 98449.

WP2 – Ethics approval has been granted through the Faculty of Health and Social Care Research Ethics Committee (FREC, FOHS 170, 15/05/2017) see appendix 3.

WP3+4 – Will require ethics approval from FREC and through IRAS application requiring approval from the National Research Ethics Service (NRES) and Health Research Authority (HRA). During the identification period only members of the research team who are involved in the clinical care of the children will have access to medical information or Trust held databases.

Informed consent and assent will be gained prior to any data collection and participants will have time to read and consider age appropriate information leaflets prior to consenting to be involved. Participants are able to withdraw at any point. All data will be anonymized and identifiable through a code only (refer to section 10 – data protection NIHR fellowship contract).

The research management team and steering committee team will also oversee the project and this will include a parent representative.

How will you manage copyright and Intellectual Property Rights (IPR) issues?

The research is not expected to lead to patents.

Data will be owned by Alder Hey Children's NHS Foundation Trust and IPR issues will adhere to Trust policy with guidance from the NIHR according to contractual requirements of the fellowship (signed by Alder Hey, supported by EHU - Fellowship number ICA-CDRF-2016-02-065 refer to section 16 of contract)

STORAGE AND BACKUP

How will the data be stored and backed up during the research?

WP1 – Individual scoring forms are stored in a locked cabinet in a locked room at the sponsor site as per details of the IRAS application. CRFs are stored similarly in the site specific file. Regarding individual consent forms, copies are placed in the participant's physiotherapy notes and the hard copies are placed in the master site file which is retained in the Oncology Research Office in a locked cabinet. Study documents will be kept for 10 years in line with Trust Policy. Electronic data (outcome measure scores) are held on a database stored on password protected encrypted servers at the sponsor site and backed up on an external encrypted hard drive.

The above procedures will apply to participant data for WP4 also, with the PI for each site retaining individual data collection sheets and participants consents in respective site files. The research administrator at the sponsor site will be responsible for the inputting of the CRF for both sites.

WP2 – Initial data is held on the Survey Monkey site (account password protected). Any exported data will be stored on password protected encrypted servers at the sponsor site and backed up on an external encrypted hard drive. Data will be stored for 10 years as per Edge Hill University policy.

WP3+4 – Qualitative data generated from workshops and interviews will be stored similarly. With electronic data gathered (pseudo-anonymised transcripts/field notes) stored on password protected encrypted servers at the sponsor site and backed up on an external encrypted hard drive.

How will you manage access and security?

All electronic data will be password protected and stored on a secure network computer. The external hard drive used to back up data will be encrypted and all files password protected.

All paper documents relating to the study will be stored in a locked cabinet in a locked or pass protected room at the sponsor site (and site specific documents for WP4 stored similarly at additional sites).

SELECTION AND PRESERVATION

Which data are of long-term value and should be retained, shared, and/or preserved?

Clinical data will be kept in line with details on IRAS application following MRC guidelines on personal information in medical research (refer to section 10 NIHR fellowship contract). Study documents will be retained for 10 years in accordance with Trust policy.

What is the long-term preservation plan for the dataset?

Primary data will be stored on the sponsor site network and will confidential and pseudo-anonymised. NIHR recommended research repository will be used to deposit both qualitative and quantitative data as applicable (refer to section 11 NIHR fellowship contract).

DATA SHARING

How will you share the data?

Any academic material will be shared in line with the NIHRs guidelines and in accordance with Trust policy (refer to section 11 of the NIHR fellowship contract)

Are any restrictions on data sharing required?

Data which underpins any publication will be made available at the time of publication

All data sharing will adhere to the contractual requirements detailed by the NIHR and in line with Trust policy. It is acknowledged the NIHR are currently developing their data management/open access policy.

RESPONSIBILITIES AND RESOURCES

Who will be responsible for data management?

Principal Investigator: Helen Hartley with support of the research team and the host Trust as main sponsor of the fellowship.

What resources will you require to deliver your plan?

The support of the supervisory team will be required as will access to NIHR/University appropriate research repositories.

Appendix 53 – Screening and recruitment log for R+D

Screening Recruitment and Participation Activity Report for ASPECT Study

Screening Activity Summary

Patients screened to date	Date period
11	09/04/2018 to 20/01/2020

Pre-Screening

	Aug 18 – March 19	**Apr 19 – Dec 19**	**DUE JAN 20**
Children with Post fossa tumour 1-3 yrs post-surgery	n=32	N=12	
Exc age range	n=1	N=4	
Exc SARA too low	n=12	N=2	
Exc poor prognosis/relapse	n=9	N=2	
Exc out of area	n=2	N=1	
Approach for screening	**N=8**	**N=3**	

Screening

	Total Participants Recruited	**Children Screened Not eligible**	**Screened Children Declined**	**Received study information –to be Followed up**	**Total number of Children screened**
April 18 – Jun 18	**0**	**0**	**0**	**0**	**0**
Jul 18 - Sept 18	**0**	**1**	**2**	**1**	**6**
Oct 18 – Dec 18	**2**	**0**	**1**	**0**	**7**
Jan 19 – Mar 19	**2**	**0**	**0**	**0**	**7**
April 19 – Jun 19	**3**	**0**	**1**	**0**	**11**
Jul 19 - Sept 19	**5**	**0**	**0**	**0**	**0**
Oct 19 – Dec 19	**5**	**0**	**0**	**0**	**0**
Jan 20	**6**	**0**	**0**	**0**	**11**
Feb 20					

Participant Recruitment Summary

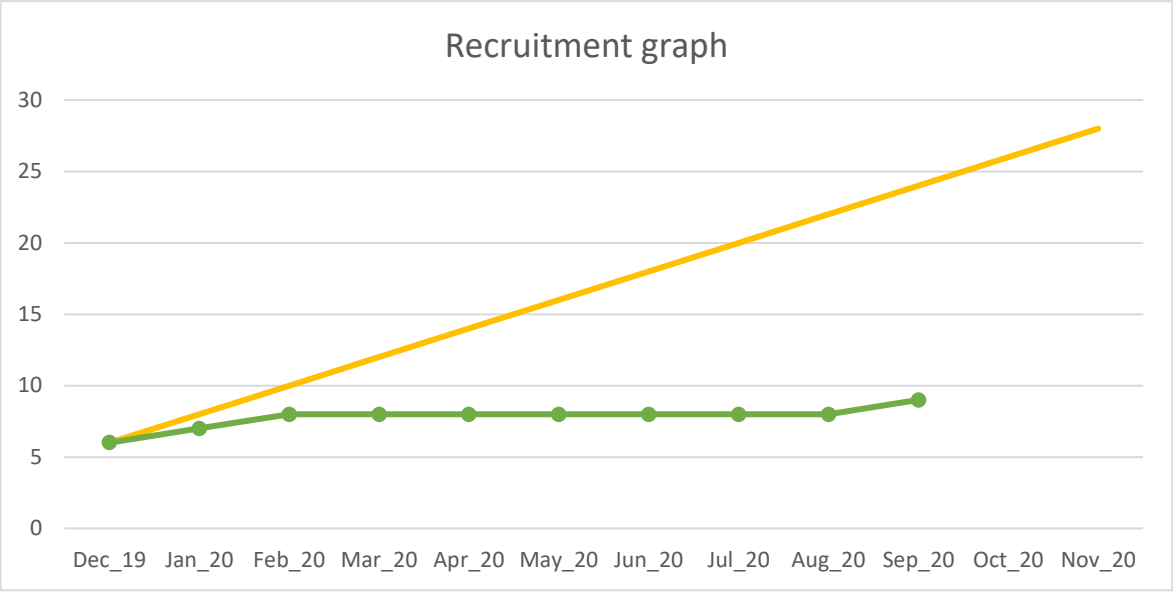
Participant	Outcome	Reason
A01	Completed and parent also recruited for interviews	
A02	Completed and parent also recruited for interviews	
A03	Completed and parent also recruited for interviews	
A04	Completed (but 2 out of 3 assessments only)	family cancelled appt for second assessment
A05	Completed – parent recruited for interview – not yet undertaken	
A06	Ongoing	

Not Eligible Screens – Key Themes
SARA score under 2

Expressions of Interest Summary

Declines - Key Themes		
Travel time	Time commitment if received intervention arm	Prefers to do own activities at home and not attend hospital for intervention

Appendix 54 – Recruitment graph



Appendix 55 – Risk Assessment for ASPECT due to impact of COVID-19

ASPECT Study – Implications of the COVID-19 outbreak (risk assessment) (25.3.2020)

Review date (1): 23rd April 2020 (supervision meeting)
Review date (2): 21st May 2020 (supervision meeting)
Review date (3): 18th June 2020 (supervision meeting)

WP4 RCT Feasibility Trial		
Impact	Actions Completed to date	Further actions
Recruitment In line with local and national recommendations ASPECT study classed as Cat 2 Study – as such recruitment is suspended across all sites Opening of GNCH site is also suspended	All PI at each site informed CRN informed	Inform NIHR by way of annual report - **Completed**
Reassessment date 23.4.20	NIHR informed via annual report	HH to liaise with GNCH to ensure all possible progress up to point of opening is completed - **Completed**
Reassessment date 21.5.20	Contact with GNCH completed, they report all stages of approval completed up to point of opening which is on hold	Compose letter for discussion at upcoming research meeting re rationale for re-opening. (Need to consider risk factors for vulnerable children and steps to reduce this) - **Completed**
Reassessment date 18.6.20	Further reopening assessment information sent to SOC	Email SOC to check re progress of decision on WP4 Contact all other sites to enquire re reopening process
Follow Up 2 children have final assessments due within the next 6 weeks. Plan to offer telephone consultation to complete subjective measures No children receiving intervention therefore no immediate clinical risk associated with study equipment/vulnerable population attending site	Liaison with relevant local sites	Discussion with supervisory team regarding how long can extend time frame for objective measures – **Completed**

Reassessment date 23.4.20	Discussion in supervision re options to facilitate video option for reassessment and implications of this	Email R+D re process of ?REC amendment to enable potential for video option for reassessments Look into risk assessment requirements for video Ax - **Completed**
Reassessment date 21.5.20	Substantial amendment submitted to request approval for virtual assessments for participant already recruited (and for any future participants)	Await REC and HRA response
Reassessment date 18.6.20	Nil new categorisation received but no decision as yet	Await REC and HRA response
Finance NIHR have confirmed payments for fellowship will continue as planned currently		Comment on NIHR report HH to discuss with finance w/c 23/3. - **Completed**
Reassessment date 23.4.20	Meeting with finance 24.3.20	A/w finance feedback expected May prior to submission of NIHR finance report in June - **Outstanding**
Reassessment date 21.5.20	Nil further	Chase finance feedback
Reassessment date 18.6.20	Provisional finance report received and meeting scheduled to check outstanding queries	Meeting with finance 18.6.20 (BC and HH)
WP1 CARS Study		
Recruitment As non-portfolio study no formal categorisation. Clinics cancelled currently, therefore will hold reconsent for previously known participants. New patients who are being managed by acute therapy team are still eligible for consent but this will be determined on an individual basis dependent on clinician capacity		

Reassessment date 23.4.20 Reassessment date 21.5.20 Reassessment date 18.6.20	Confirmed with supervisory team current plan remains appropriate Identification completed up to current date Further information sent to R+D for SOC to review reopening **Study now reopened by R+D**	Continue to identify potential participants for approach at later date as appropriate – **completed to date keep as ongoing action** Request approval to reopen as new participants approached as inpatients (no additional visits required) and therapy capacity improving - completed Identify potential participants missed during COVID-19 Reopen to recruitment
Ongoing assessments may still be completed if child is undergoing acute rehabilitation. This will be prioritised by individual staff members. Will not be completed in context of outpatient or clinic visits (unless child is attending on site and assessments indicated as part of routine practice) Reassessment date 23.4.20 Reassessment date 21.5.20 Reassessment date 18.6.20	Confirmed with supervisory team current plan remains appropriate Ongoing data collection for children already recruited who were on site has been continuing Ongoing data collection	Ongoing data collection as appropriate for children already on site as part of routine practice – **completed to date keep as ongoing action (either on site or virtual if undertaken as routine care)** Ongoing data collection as part of routine practice
Fellowship time commitment		
HH to work clinically within acute neurosciences team within first instance and then likely to move to PICU setting as required.	Task prioritised e.g. required reports submitted (Annual progress and NIHR reports all to be submitted w/c 23/3) then no deadline	Liaise with NIHR and management re implications of move to clinical time.

Minimal fellowship time commitment anticipated over next 8 weeks. Reassessment date 23.4.20 Reassessment date 21.5.20 Reassessment date 18.6.20	tasks are pending currently. Currently completing 75% clinical time and 25% fellowship commitment Moved to 50% clinical time and 50% fellowship time. Steering group update sent out Continuing with 50:50 split	Log time lost to clinical work as evidence of changed commitments Ongoing log of clinical/fellowship time - **ongoing** Email Bernie re latest NIHR guidance to ensure no further immediate action required - **completed** Defer steering group meeting but email update for comments as required - **completed** Consider date for move to original working pattern i.e. 25% clinical and 75% fellowship Return to 25% clinical and 75% fellowship on reopening of WP4

Appendix 56 – Request to reopen studies following COVID-19

Alder Hey Sponsored Study Restart Assessment Form

In accordance with national guidance, the commencing of study activity that has been paused as a result of covid-19 is dependent on a number of pre-conditions being met.

Study Title: Aspect

IRAS Number: 227917

1. Study Summary	
Pre-conditions for re-start	Rationale/Comments
1. Viability Only research that is still viable should restart/start - Scientific, clinical, financial and practical considerations - Can study objectives be met within the timeframes	It is noted children who would be eligible for this study have seen their current usual care community therapy provision reduce or stop during this period due to redeployment of community therapy staff, therefore, this trial will provide access to 'better than current care'. Opening will be phased, with lowest risk children (surgery only) who are attending the hospital site for usual practice appointments being eligible for phase 1. Children who have received chemotherapy or radiotherapy in the last 6 months would be considered as phase 2 as they are in a higher risk category. Ongoing advice will be sought by the local oncology team and CCLG regarding any changes to this categorisation. Following SOC review the plans for this phased opening would be discussed with wider steering group (includes parents' views) before implementing. Funding remains in place for the study until 31.3.2021 as part of NIHR fellowship. REC approval for recruitment remains in place until 31.12.2020.
2. Safety Research should only restart when safe to do so Safety considerations should include; - Risk of exposure to covid-19 - Local site policies in respect of covid-19 - An assessment of the need for patient testing for covid -19 and the requirement or PPE - site compliance with protocol and regulatory requirements	Clear thinking about this phased opening include the following: • Initial approach to potential families can be undertaken during a usual practice clinic appointment which requires on site attendance. • Minimisation of subsequent trial-related visits to the hospital site. A submission of amendment to REC/HRA requesting approval for virtual assessment was submitted on 21.5.20. Limited intervention visits

	may be required on site (depending on randomisation and child's/parents' ability to undertake training at home). • Any on-site visits will be subject to current Trust and Therapy local policies to minimise flow of traffic through the hospital and following PPE and cleaning guidance. (Equipment is not required to be shared between participants during the study period).
3. <u>Capacity and Site Readiness</u> The pace of restart and commencement of new studies should be commensurate with capacity and readiness in local NHS and health care settings Capacity considerations should include; - Availability/capacity of study delivery team and leadership staff (**The CRD R&D team will provide confirmation of delivery staff availability**) - Support service capacity to resume - Physical access arrangements for participants	Therapy led study and capacity is in place to continue with this study. Therapy teams are routinely involved with this population group.

3. Patient enrolment, Visits & Interactions ***patient's only option for treatment)***
Level 1 – Nationally Prioritised Urgent Public Health COVID-19 Studies Level 2 - Studies where the research protocol includes an urgent treatment or intervention without which a patient could come to harm – could be providing access to potentially life-extending treatment that would be otherwise unavailable. Level 3 – All other research
NIHR Cat 2 funded study, participants currently in the study who have outstanding assessments to be completed. Also as stated above due to reduced provision of community therapy services during this time frame this study provides access to 'better than usual care'. **a) Does this study require participants to make additional <u>onsite</u> visits <u>above</u> standard care?**
Yes
b) Where applicable please detail any changes to the methodology or study delivery which you have made to accommodate COVID-19 operational pressures (*e.g. telephone follow ups*)

Additional visits will be significantly reduced by option of virtual assessments which has been submitted as amendment to REC/HRA on 21.5.20.
Limited visits for participants recruited to the intervention group will be required at the start of the intervention, the intervention is then continued at home to further reduce hospital visits. Wherever possible these visits will be tied in with any other appointments the participant may be attending on site for.
All exit interviews are completed by phone.

c) Will any amendment be needed to be put in place before this study can reopen? (*if yes, please detail below)*

Request to reopen to recommence participant identification and complete assessments of participants already in study (if they are attending on site for other appointments).
However, await amendment approval re virtual assessments before continuing to recruit new participants.

4. Alder Hey Chief Investigator Declaration

Name: Helen Hartley

Date: 06.06.2020

Appendix 57 – CARS Paper

Title Page

Authors; H Hartley, S Lane, B Pizer, L Bunn, B Carter, E Cassidy, R Kumar

Title; Ataxia and mobility in children following surgical resection of posterior fossa tumour: A longitudinal cohort study

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Abstract

Purpose

To report the course of ataxia in children up to two years post-operatively, following surgical resection of a posterior fossa tumour (PFT).

Methods

Thirty-five children, (median age 9 years, range 4-15) having resection of PFT were assessed using the Scale for the Assessment and Rating of Ataxia (SARA), Brief Ataxia Rating Scale (BARS) and the mobility domain of the Pediatric Evaluation of Disability Index (PEDI-m) at initial post-operative period (baseline), three months, one year and two years post-operatively.

Results

Baseline median scores of the SARA and BARS were 8.5 (range 0-35.5), and 7 (0-25) respectively. Ataxia improved at three months (median SARA and BARS reduction 3.5 and 4 respectively). Additional gradual improvements in SARA were recorded at one (median reduction 2) and two years post-operatively (median reduction 0.5). Median baseline PEDI-m was 54.75 (range 15.2-100) with improvement at three months (median increase 36.95), and small improvement at one year (median increase 2.5) and two years (median increase 5.8).

Children with medulloblastoma and midline tumours (median baseline SARA 10 and 11 respectively) demonstrated more severe ataxia than children with low grade gliomas and unilateral tumours (median baseline SARA 7.5 and 6.5 respectively).

Conclusion

The largest improvement in ataxia scores and functional mobility scores is demonstrated within the first three months post-operatively but ongoing gradual improvement is observed at two years. Children with medulloblastoma and midline tumour demonstrated higher ataxia scores long term.

Keywords; Paediatrics, cerebellum, rehabilitation

Declarations;

Funding

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Conflicts of Interest

No authors have any conflict of interest.

Ethics Approval

This study was approved by the local research ethics committee (REC) and Health Research Authority IRAS ID 98449.

Consent to participate

Written informed consent was obtained from all individual participants (and/or parent/guardian) included in the study.

Consent for publication

Not applicable, no personal or identifying information included. Informed consent process included sharing of non-identifiable data.

Availability of data and material

The datasets generated during and/or analysed during this study are available from the corresponding author on reasonable request.

Code Availability

Not applicable

Introduction

Posterior fossa tumours (PFT) account for approximately 50% of all childhood brain tumours [1]. Management of PFT typically involves surgical resection, solely or in combination with adjuvant treatments such as radiotherapy and chemotherapy [2].

Ataxia is the predominant motor problem in children with PFT. Ataxia describes a number of related impairments including limb incoordination, tremor, gait disturbance, impaired balance, and oculomotor and oromotor dysfunction [3]. Approximately 60% of children with PFT demonstrate ataxia pre-operatively [4]. The severity and incidence of ataxia may increase post-operatively [5].

Evolving evidence indicates that ataxia can persist in the long term in children with PFT. Robertson et al. [5] presented initial work in this area observing that children with severe ataxia at one-month post-operatively continued to have ataxia at one year after surgery. Sønderkær et al. [6] reported that ataxia may persist at 10 years after surgery. More recent reporting with standardised outcome measures has also observed approximately 70% [7,8] of children with PFT demonstrate balance dysfunction more than one year following surgery.

Kuper et al. [9] presented one of the few studies with longitudinal data, describing the recovery of 12 children with cerebellar tumour from the early post-operative period, to reassessment at three months and one year. They noted ongoing recovery throughout the first year, although children with injury to the deep cerebellar nuclei had persistent impairment. These findings support the earlier cross-sectional study by Konzcak et al. [10].

In this paper we present a new insight into the longitudinal course of ataxia and functional mobility using standardised measures in children with PFT from the peri-operative period, initial post-operative period and up to two years post-operatively. Additionally, we explore the impact of tumour location and histology on severity of ataxia.

Methods

Design

Cohort prospective single site longitudinal study.

Participants

Children who had surgical resection of a PFT and were aged between 4 -18 years (inclusive) were eligible for inclusion. Due to the need to be able to follow the instructions required for assessment of ataxia, the lower age limit was set as 4 years old.

Procedures

Children were recruited from a single tertiary neurosurgical/oncology unit in the United Kingdom between 2012 and 2018. The study was approved by the relevant local ethics and research and development committee (IRAS ID98449).

Potential participants were identified and screened for eligibility by the neurosciences therapy team. Informed and written consent was obtained from all children and/or their parents (with child assent).

Children were assessed initially as an inpatient within one week of surgical resection (baseline), and then in an outpatient clinic setting at three months, one year and two years post-operatively. Assessments were completed by a neuro-physiotherapist trained in the use of the standardised outcome measures. A subset of participants was also assessed pre-operatively; this occurred if children were stable pre-operatively and where timing of admission and surgery allowed for pre-operative assessment.

Ataxia Outcome Measures

Children were assessed using the Scale for the Assessment and Rating of Ataxia (SARA scale) [11] and the Brief Ataxia Rating Scale (BARS scale) [12]. The SARA and the BARS are reliable and valid measures of ataxia for children with PFT [13]. The SARA is used in clinical paediatrics and has age based normative reference values [14]. It has 8 items and has a total score out of 40, with a higher score indicating more severe ataxia. Three items of the SARA (gait, stance and sitting, total 18) have been deemed the Bal-SARA [15] and particularly represent balance impairment. The BARS has 5 items and is scored out of 30, a higher score indicates more severe ataxia. Both scales are quick and easy to use based on a standard clinical examination of ataxia.

The mobility domain of the Pediatric Evaluation of Disability Index (PEDI) was also used as a functional mobility measure [16]. The PEDI is a valid and reliable functional measure in children with acquired brain injury (validated from 6 months to 7 years, although it can be used in older children with functional difficulties) [16]. It has self-care, mobility and social function sections which can be used as a whole or as stand-alone domains. It is completed by the therapist or by parental questioning. Only the mobility domain of the PEDI (PEDI-m) was collected to minimise time burden of assessment for the participants. A higher PEDI-m score (range 0 to 100) represents a better level of physical function and correlates with lower overall measures of disability.

Baseline disease descriptors

Baseline potential predictive factors of severity of ataxia were collected including tumour histology, age at diagnosis, adjuvant treatment (radiotherapy or chemotherapy) and tumour location.

Data Analysis

The data were summarised using descriptive statistics (including age at diagnosis, tumour location and tumour histology). The SARA and the BARS demonstrated similar patterns, and as the SARA is more widely used in clinical paediatrics further analysis regarding ataxia was undertaken using the SARA only.

Patterns of change in outcome measures were therefore explored graphically for the SARA and the PEDI-m. Participants were stratified by putative predictive factors of tumour histology (medulloblastoma versus low grade glioma) and tumour location. The PEDI is normative-referenced between 6 months and 7.5 years. In line with recommendations, raw scores were converted to scaled scores to enable the use of the PEDI-m in children over the age of 7.5 years.

Results

Study sample

Thirty-five participants were recruited to the study. Participant characteristics are detailed in Table 1.

Table 1 – Participant characteristics at baseline (n=35)

Characteristic	Value
Gender (n)	

Male Female	21 14
Age at time of recruitment (years) Median (range)	 9, (4-15)
Histology (n) Low grade glioma Medulloblastoma Ependymoma Other (e.g. Schwannoma)	 17 11 4 3
Location (n) Midline Unilateral	 23 12

Ataxia Outcome Measures

Descriptive analysis of the outcome measures is presented in Table 2. The SARA range at baseline was 0 to 35.5. The BARS range at baseline was 0 to 25. A higher SARA (out of 40) and BARS score (out of 30) represents more severe ataxia. The SARA and BARS scores were in agreement demonstrating a similar trend and therefore for the rest of the results as detailed in the data analysis plan only the SARA is presented alongside the PEDI-m. The PEDI-m range at baseline was 15.2-100 (higher score representing better functional mobility, maximum score 100). A ceiling effect of the PEDI-m is noted with 39% of children reaching the maximum score of 100 at one year post-operatively

Table 2 – Participant ataxia and mobility scores

	Pre- operative score n=22	Baseline n=35	3 months n=31 (n=4 missing)	1-year n=33 (n=1 missing, n=1 died)	2-year n=31 (n=2 missing, n=2 died).
SARA Group median (IQR) range	6 (8.5) (0-24)	8.5 (9.5) 0-35.5	5 (4.5) 0-30	3 (6) 0-28.5	2.5 (5) 0-16.5
Bal-SARA Group median (IQR) range	3 (5.25) 0-16	5 (5) 0-18	2 (2) 0-17	1 (3) 0-16	1 (3) 0-8
BARS Group median (IQR) Range		7 (10.5) 0-25	3 (3.25) 0-24	3 (5) 0-24	2 (5) 0-16
PEDI-m Group median (IQR) range		54.75 (30.9) 15.2-100	91.7 (20.2) 20.9-100	94.2 (20.2) 30.6-100	100 (16.15) 47-100

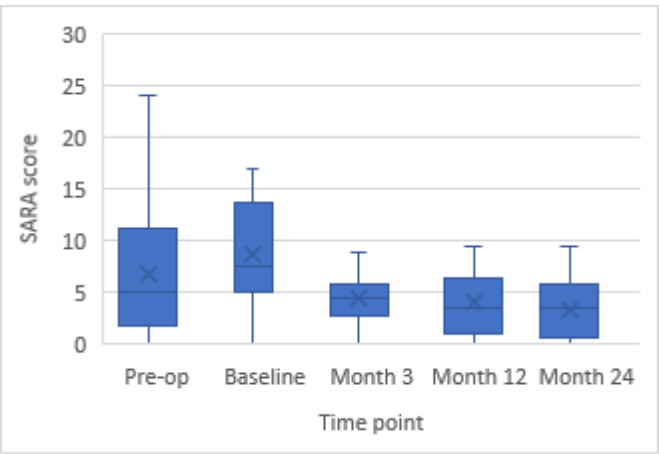
Twenty-two children were also assessed pre-operatively using the SARA scale. There was an initial increase in SARA post-operatively (worsening ataxia) followed by improvement on average for the group. The

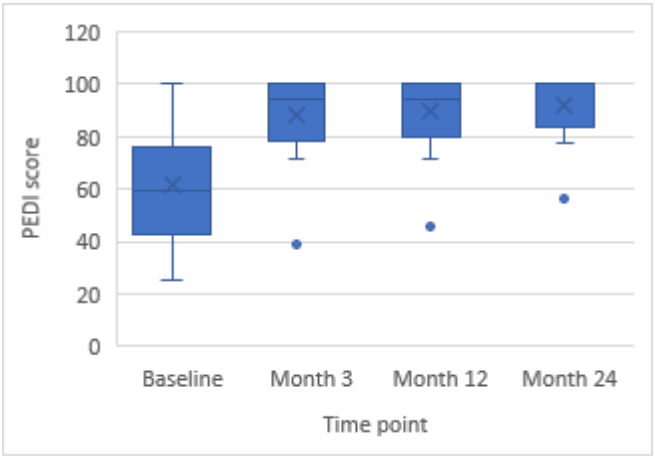
ataxia scores at three months post-operatively are lower (better) than the pre-operative assessment scores, indicating improvement in ataxia three months after surgery. At two years post-operatively ataxia severity had reduced by half of the pre-operative level (median values for the overall sub-group).

The change in Bal-SARA represents a large proportion of the initial change in SARA score. The Bal-SARA includes gait, stance and sitting items of the SARA scale.

Group median scores for the SARA and PEDI-m which graphically illustrate Table 2 are represented in Figure 1. (Alternative graphical representation of line graphs for figures 1-3 are available in supplementary material).

Fig. 1 Group median SARA and PEDI-m scores over time for children (n=35) assessed up to 2 years post-operatively



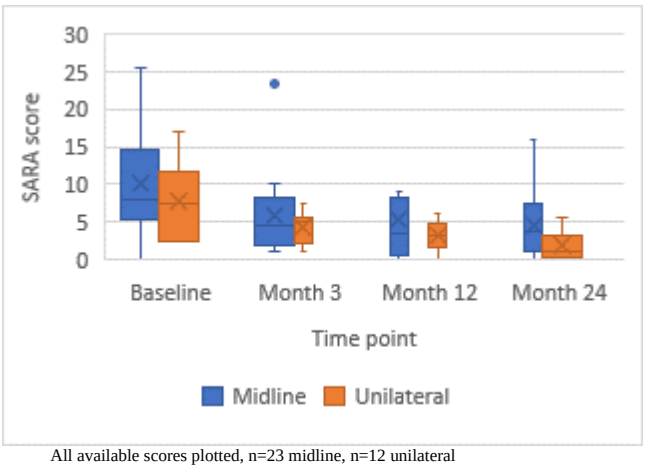


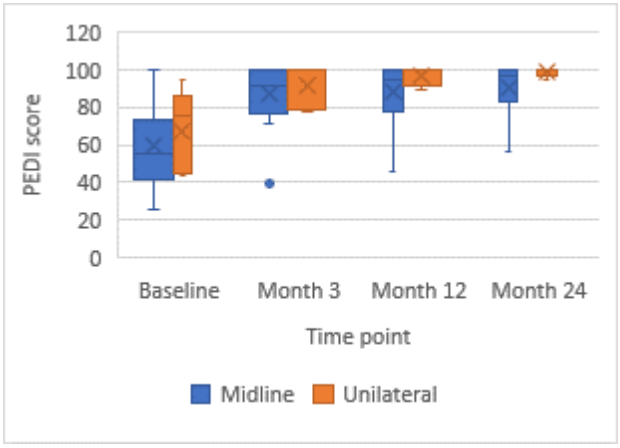
All available scores plotted, n=22 SARA scores for pre-operative group

Effect of tumour location

Further analysis was completed to compare change over time for outcome measures dependent on tumour location (Figure 2).

Fig. 2 Group median SARA and PEDI-m scores for children (n=35), dependent upon tumour location





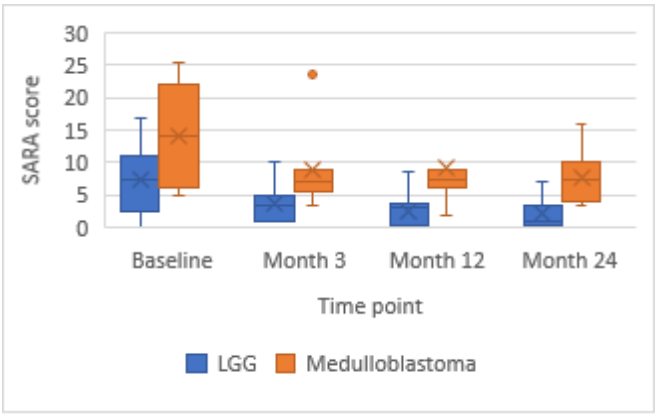
All available scores plotted, n=23 midline, n=12 unilateral

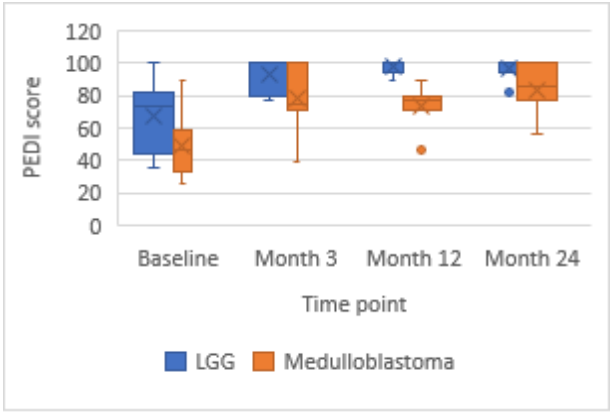
A similar trajectory for both tumour locations was noted, however, children with unilateral tumours demonstrated lower SARA scores than those with midline tumours, indicating less ataxia throughout all time points. The change in PEDI-m scores demonstrated the same trajectory as previously noted, with rapid increase in scores between baseline and three months, although there is less difference in scores between tumour location. The ceiling effect of the PEDI-m is observed.

Effect of tumour histology

Further analysis was completed to determine whether changes in outcome measure score were dependent on tumour histology. The two most common tumour histologies, medulloblastoma (n=11) versus low grade glioma (n=17), are presented for post-operative timepoints.

Fig. 3 Group Median scores of SARA and PEDI-m scores for children (n=28), dependent upon tumour histology





All available scores plotted, n=17 LGG, n=11 medulloblastoma

Although both tumour types follow a similar trajectory, i.e. rapid drop in ataxia from baseline to three months post-operatively, children with medulloblastoma had higher SARA scores (more severe ataxia) and lower PEDI-m scores (more mobility function impairment) than children with low grade gliomas (Figure 3). The gap in ataxia scores appears to widen after one year; children with medulloblastoma had higher ataxia severity at two years post-operatively. It is noted the gap between the tumour histology groups is wider than the graphs comparing tumour location.

Both the SARA and PEDI-m appear to be able to distinguish between the two tumour types. Again, there is a ceiling effect for the PEDI-m.

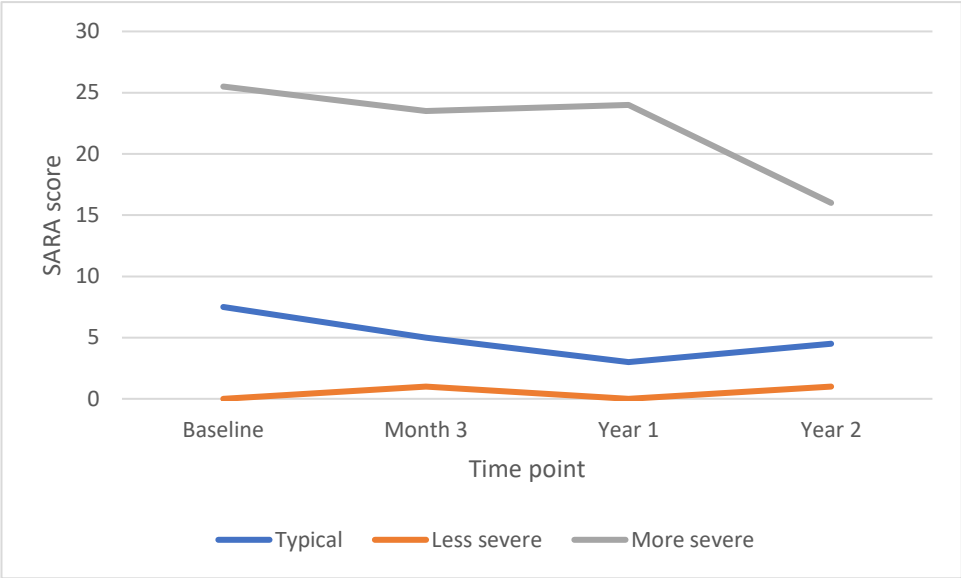
Individual Change Scores

Considering individual change scores per participant there was an initial worsening of ataxia for most participants, from pre to post-operatively with a median change in SARA of +3.5, with a large range of change from -18 to +18.5. Post-operatively from baseline to three months following surgery there was a median change of -4.5 for the SARA (improvement). The range of change for individual participants was -16.5 to +2. Additional gradual improvements for SARA individual change scores were recorded at one year with a median change of -1 (range -4.5 to +2.5) and two years with a median change of -0.5 (range -4.5 to +13.5).

Return of functional mobility behaved similarly, with a rapid increase in individual change scores, median change +27.8, (range -9 to +64.1) from baseline to three months post-operatively, indicating an improvement in mobility, with a plateau at one and two years post operatively, median individual change score of 0.

The large range in individual change scores highlights individual variability. This is illustrated in Figure 4 where three participants with different individual trajectories of ataxia are presented, one participant demonstrated a typical course, one participant demonstrated more severe ataxia with later improvement and one participant demonstrated minimal ataxia with consistently low scores.

Fig. 4 Example of individual participant trajectory of ataxia (for 3 participants)



Discussion

This is the largest published longitudinal study to focus specifically on ataxia in children with PFT and the first to report the course of ataxia up to two years after surgery including pre- and post-operative scores. Putative factors (tumour histology and location) that may predict the severity and course of long-term ataxia were also identified.

The most rapid improvement in ataxia was noted in the first three post-operative months. Much smaller change was noted thereafter up to two years post-operatively. Although the minimally clinically important difference (MCID) for the SARA in children has not been determined, the MCID for adults has been reported as 1.1 [17]. The MCID might be higher in children with increased variability in performance (particularly in younger children), however, the group median change was more than three times the adult suggested value (3.5 between baseline and three months post-operatively), which highlights the potential clinical significance of this change. A threshold of change of 2.0 or more in SARA has been suggested to allow for physiological fluctuation in healthy children [14]. The change seen in this study is higher than this. The Bal-SARA subset appears to account for a large proportion of this change, indicating that balance in particular rather than limb coordination improves in the initial post-operative period.

For the PEDI-m a rapid improvement in mobility was also noted at the three-month assessment (exceeding the MCID suggested by Iyer et al. [18] of 11%), followed by minimal change after this point, although a ceiling

effect for the PEDI-m was noted in this population (13 of the children scored a maximum of 100 at one year post-operatively). This means ongoing higher level mobility problems may not be detected by this tool. Caregiver assistance scores for the PEDI could be used in future studies as this might highlight more subtle change, such as the child being able to do a task with less assistance, which might have a meaningful impact on family life. Future research might usefully consider alternative outcome measures examining balance impairment such as the Paediatric Balance Scale [19] and measures of participation.

Analysis of a subset of children who were assessed pre-operatively demonstrated an initial increase in ataxia post-operatively, followed by a drop below the pre-operative level by the 3-month assessment time point. Although it is known that approximately 60% of children will present with ataxia pre-operatively [4], this is the first time that the change during this time period has been quantified, and it would be of value to confirm these findings with a larger sample.

SARA scores are age-dependent in healthy children [14,20]. However, due to the small number of participants in this study it was not possible to consider age formally as a confounding factor in the analysis. Although children may not reach the adult optimum for the SARA (and BARS) scores until the age of 10, Lawerman et al. [14] suggested that the median total SARA score is under 1.5 in healthy children from age 6 to 10 years. Additionally, between each age year increment only a small decrease of 0.5-1 is expected on the SARA (e.g. median SARA score in healthy 6 year olds is 1.5, in 7 year olds, 0.5). This would suggest that the large changes seen in the first three months following surgery are consistent with recovery and repair of brain function and not just age-related maturational changes which occur over a longer time course.

The pattern of change reported in this study is supported by results from a longitudinal study which measured function in 12 children with PFT (age 6-17 years) who were followed up to one-year postoperatively [9]. A reduction in ataxia score was observed (using the International Cooperative Ataxia Rating Scale ICARS) from the acute post-operative period to one year after surgery, with a statistically significant reduction in the first three months, but not from three months to one year, similar to findings from our study. Kuper et al.. [9] observed an improvement between three months and one year after surgery in upper limb motor function and body sway measured using instrumented motion analysis.

Kuper et al.. [9] suggested that reduction in oedema affecting the deep cerebellar nuclei was a predictor of early functional recovery. If the resolution of oedema happens over days to weeks, an additional assessment

time point at one month, could demonstrate if the time of most rapid change (improvement) corresponds with the expected resolution of oedema. If this is not demonstrated, other mechanisms such as axonal sprouting and long-term potentiation would need to be considered to explain recovery in the first three months (acute phase). The recovery trajectory identified in the present study is consistent with studies of children with acquired brain injury (from other pathologies) which also indicate that the most rapid change occurs in the first 6 months post neurological insult [21].

Children with medulloblastoma and those with midline tumours demonstrated higher ataxia scores (and lower functional mobility scores) throughout the trajectory of their recovery. This is in line with other studies reporting that children with medulloblastoma have a higher incidence of ataxia and cerebellar mutism syndrome than children with other tumour types [5,22-25]. In contrast, children with low grade gliomas (LGG) (predominantly pilocytic astrocytomas) typically demonstrated lower ataxia scores. These findings are further supported by research that reports children with LGG most often have mild cerebellar dysfunction [26].

It is difficult to determine the influence of tumour histology compared with tumour location on ataxia severity, as there is an inherent link between the two factors: medulloblastoma more often being midline than lateralised in the cerebellum and LGG showing the converse relationship. Lesions to the deep cerebellar nuclei and inferior vermis, which are structures at or close to the midline, and the involvement of the efferent cerebello-thalamo-cerebral tract have been linked with persistent motor deficit in children [10,24,27]. Future research should consider utilising detailed imaging of specific tumour location, cerebellar and tumour volume as predictors of severity of ataxia.

Findings from this study show a wider gap in ataxia scores depending on tumour histology than observed due to tumour location, suggesting that histology differentiates the strata of participants better than tumour location. Despite not being independent factors, this indicates that anatomical predilection of tumour histology is not the whole answer, and other elements should be considered, the most obvious being the need for adjuvant oncology treatment i.e. radiotherapy and chemotherapy for children with medulloblastomas. An increase in SARA score was noted for children with medulloblastoma after three months, which may be caused by intense adjuvant treatment with radiotherapy and chemotherapy in this period [7]. Typically, a six-week course of radiotherapy is commenced within one month of surgery, and maintenance chemotherapy begins six weeks following this. Peripheral neuropathy which is a known side effect of chemotherapy can impair postural control strategies and result in functional balance problems [28]. Exploring the specific impact of adjuvant therapy

with a larger population could improve understanding of its impact, e.g., comparing the trajectory of ataxia in children who solely had surgery with those who had surgery and radiotherapy, and those who had surgery and chemotherapy.

The small number of children with severe ataxia (SARA greater than 14 [13]) in this study meant it was not possible to compare the pattern of change across the trajectories of children with severe ataxia with those with mild/moderate ataxia. This analysis should be undertaken in future research to determine if there is any difference in recovery. Mapping individual trajectories (as in Figure 4) with a larger data set might also be of value to identify characteristics of participants who show potential for ongoing improvement and to help focus rehabilitation interventions. Identifying children who have less potential to improve would also be of value in counselling families.

This is the largest study to date reporting longitudinal ataxia severity in children with PFT. The strengths of this study include a prospective design using standardised validated outcome measures [13] over a two-year period. The number of participants remains relatively small particularly for subgroup analysis. A further limitation is that the children were recruited from one tertiary site.

Our study provides information about the long-term course of ataxia in children following surgical resection for PFT. Children often have worse ataxia after surgery, before improving to better than they were prior to surgery. Children with medulloblastoma and midline tumours have more long-term balance and coordination problems compared to children with LGG or unilateral tumours. The most rapid improvement was seen in the first three months postoperatively followed by a small change up to two years post-operatively. Any late changes do not appear to be explained simply by developmental maturation of cerebellar function especially in adolescents, though the impact of age should be examined further.

Although the findings would benefit from further confirmation with a larger dataset, they demonstrate the need to examine the potential of targeted rehabilitation interventions more than one year post-operatively when some children otherwise typically appear to demonstrate minimal change.

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