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Lucy Beasant

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree Doctor of Philosophy in the Bristol Medical School

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Abstract

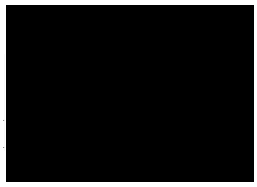
Randomised controlled trials (RCTs) rely on effective recruitment and retention for successful completion. Potential trial participants' preference for a treatment (trial intervention) can affect recruitment, post randomisation drop-out and adherence to intervention groups in adult RCTs, but little is known about how they may affect paediatric trials. Communication of trial information in paediatric trial settings is complex as it needs to accommodate the parent's as well as young person's perspective, whilst at the same time maintaining high standards of trial conduct. This PhD explored how treatment preferences influenced recruitment and participation in paediatric RCTs by undertaking a systematic review of the literature and embedding qualitative research in four paediatric trials.

The systematic literature review focused on paediatric RCTs and qualitative studies that reported the treatment preferences of children and young people aged 0-17 years, and their parents. Fifty-two papers were identified, twelve of which contained qualitative data. CONSORT figures reporting decline or withdrawal from trials due to treatment preference were tabulated and discussed descriptively. Techniques of meta-ethnography were drawn on to evaluate qualitative data. The systematic review showed treatment preferences acting as a barrier to recruitment to paediatric RCTs, particularly from a parental perspective. Parents' understanding of trial processes and perceptions of the benefits and risks associated with treatments promoted discussion of preference. Few RCT papers reported the views of young people in relation to preference for treatment.

Qualitative methods were embedded in three chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) trials, and one surgical trial for acute, uncomplicated appendicitis. The QuinteT Recruitment Intervention (QRI) has been embedded successfully in adult RCTs to identify and address recruitment difficulties with the intention to optimise informed decision-making and recruitment. Methods and approaches from the QRI (audio-recorded recruitment consultations, interviews, recruiter training) were employed in the present research to explore the treatment preferences of young people, their parents, and to discuss issues of equipoise with recruiting health professionals. Data analyses drew on techniques of constant comparison, content and thematic analysis. All four RCTs were able to successfully recruit paediatric participants, but preference for treatment was a consistent reason for trial decline, post randomisation drop-out and discontinued treatment in the four trials under investigation. Young people and their parents expressed treatment preferences when considering RCT participation in all four trials. However, young people were less likely to express preferences than their parents. The views and equipoise of those recruiting and treating patients influenced families at all stages of recruitment, and during trial participation. Providing training for recruiters and wider clinical teams that promoted communicating equipoise, and the exploration of preference during discussions with families, had a positive effect on observed recruitment practices. More efforts are now needed to understand preference for treatment in paediatric RCT settings, particularly in relation to the impact on trial retention and the treatment outcomes under investigation.

Authors declaration

I declare that this work was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and has not been submitted for any other academic award. Except where indicated by specific reference in the text, this is all the candidate's own work. Work done in collaboration with, or with the assistance of others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed  Date: 29/11/2019

With special thanks to my mum Christine,

Auntie Jean, Becky, Nige, Rachel and Debbie.

I dedicate this thesis to my Auntie Pat

xxxx

Declaration

I would like to thank the following individuals for their assistance with the work carried out in this thesis:

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Contribution Statement

Harry Apperley: Contribution to systematic review: Title and abstract screen.

Amberley Brigden: Contribution to systematic review: Title and abstract screen, full text review, data extraction, critical appraisal of qualitative articles, and review of meta-ethnographic third order constructs. Double coded MAGENTA interview data.

Sarah Dawson: Contribution to systematic review: Database search strategy guidance and removal of duplicate papers using Cochrane Register of Studies (desktop version 2015).

Daisy Gaunt: Reviewed Section 1.3.2: Trial design.

Nigel Hall: Chief investigator of the CONTRACT trial. Assisted with the development of CONTRACT recruitment training sessions and associated documentation. Reviewed Chapter 2: Conditions under investigation in this thesis: Acute uncomplicated appendicitis.

Tiffany Keep: Contribution to systematic review: Title and abstract screen.

Hayley King: Contribution to systematic review: Full text review and data extraction.

Ryan Langdon: Contribution to systematic review: Full text review and data extraction.

Rachel Murray: FITNET-NHS: Conducted interviews with families.
Antonia Northam: Contribution to systematic review: Title and abstract screen.

Roxanne Parslow: Contribution to systematic review: Title and abstract screen, full text review and data extraction, critical appraisal of qualitative articles and review of meta-ethnographic third order constructs. FITNET-NHS: Conducted interviews with families and health professionals. Double coded interview and recruitment consultation data. Assisted with the development of FITNET-NHS recruitment training sessions and associated documentation.

Frances Sherratt: CONTRACT: Conducted interviews with families and health professionals. Double coded interview and recruitment consultation data.

Adam Trist: MAGENTA: Conducted interviews with families. Double coded interview data.

Victoria Vilenchik: MAGENTA: Conducted interviews with families.

Charlotte Wray: Contribution to systematic review: Title and abstract screen and full text review. MAGENTA: Conducted interviews with health professionals.

Lucy Beasant contribution statement RCT interviews:

50 (54%) of the interviews conducted with families

Trial	Total number of interviews	Total conducted by LB
SMILE	13	13 (100%)
MAGENTA	32	21 (66%)
FITNET-NHS	20	0 (0%)
CONTRACT	28	16 (57%)

34 (55%) of the interviews conducted with health professionals

Trial	Total number of interviews	Total conducted by LB
SMILE	n/a	n/a
MAGENTA	12	7 (58%)
FITNET-NHS	10	0 (0%)
CONTRACT	40	27 (68%)

Publications

Hutchings N, Wood W, Reading I, Walker E, Blazeby JM, van't Hoff W et al. CONTRACT Study - CONservative TReatment of Appendicitis in Children (feasibility): study protocol for a randomised controlled Trial. Trials. 2018 Mar 2;19. 153. Available from, DOI: 10.1186/s13063-018-2520-z

Baos S, Brigden A, Anderson E, Hollingworth W, Price S, Mills N et al. Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to Activity Management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial. Trials. 2018 Feb 22;19. 136. Available from, DOI: 10.1186/s13063-018-2500-3

Crawley EM, Gaunt DM, Garfield K, Hollingworth W, Sterne JAC, Beasant L et al. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. Archives of Disease in Childhood. 2017 Sep 20. Available from, DOI: 10.1136/archdischild-2017-313375

Sherratt F, Beasant L, Blazeby J, Young B, Crawley E. Development of a core outcome set to determine the overall treatment success of acute uncomplicated appendicitis in children: a study protocol. BMJ Paediatrics Open. 2017;1(1). e000151. Available from, DOI: 10.1136/bmjpo-2017-000151

Brigden A, Beasant L, Hollingworth W, Metcalfe C, Gaunt D, Mills N et al. Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: study protocol. BMJ Open. 2016 Jul;6(7). e011255. Available from, DOI: 10.1136/bmjopen-2016-011255

Beasant L, Mills N, Crawley E. The treatment preferences of adolescents and their parents, what has the smile RCT shown us? SMILE: specialist medical intervention and lightning evaluation: Trials. 2015; 16 (Suppl 2): Published online 2015 Nov 16. 2015. Available from, DOI: 10.1186/1745-6215-16-S2-P71

Beasant L, Brigden A, Parslow R. M, Apperley H, Keep T, Northam A, Wray C, King H, Langdon R, Mills N, Young B, Crawley E. *Treatment preference and recruitment to pediatric RCTs: A systematic review.* Contemp Clin Trials Commun, 2019. **14**: p. 100335..

Conference poster presentations

Society for Clinical Trials Conference, Portland, USA 2018: Treatment preference in pediatric randomised clinical trials: systematic review and qualitative synthesis.

International Clinical Trials Methodology Conference and the 38th Annual Meeting of the Society for Clinical Trials, Liverpool 2017: Treatment preference and recruitment to a paediatric randomised controlled trial: Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA).

Research Without Boarders, Bristol 2016: Investigating the effect of treatment preferences on recruitment and retention to paediatric trials.

International Clinical Trials Methodology Conference, Liverpool 2015: The treatment preferences of adolescents and their parents, what has the SMILE RCT shown us? SMILE: Specialist Medical Intervention and Lightning Evaluation.

Intervention versus treatment

The terms ‘intervention’, more specifically ‘trial intervention’ or ‘intervention group’ were used interchangeably with the terms ‘treatment’ and ‘treatment preference’ during the writing of this thesis, to refer to interventions offered and/or preferred in a randomised controlled trial context. I did this because authors and families typically referred to trial ‘interventions’ as ‘treatments’, and because the area under investigation is generally referred to as ‘treatment preference’ in the wider literature.

Children and young people

In this thesis children and young people under the age of 18 years will collectively be referred to as ‘young people’ or ‘young person’ throughout. The majority of young people who participated in this research were aged from 8 – 17 years and were involved in making decisions about their involvement in the research studies. The terms ‘children’, ‘child’ or adolescent have been used when directly quoting the views of other authors (Chapter 1), parents and health professionals (Chapters 4 and 5), or when referring to younger children in the CONTRACT trial (aged 4-7 years) who might have lacked the developmental maturity and understanding to make informed decisions about trial participation for themselves. [1]

Contents

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List of Abbreviations

AM	Activity management
BJC	British Journal of Cancer
BJOG	British Journal of Obstetrics and Gynaecology
BJS	British Journal of Surgery
BMJ	British Medical Journal
CBT	Cognitive Behavioural Therapy
CCD	Comprehensive Cohort Design
CFS/ME	Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis
CI	Chief Investigator
CRS	Cochrane Register of Studies
CONSORT	CONsolidated Standards Of Reporting Trials
CONTRACT	CONservative TReatment of Appendicitis in Children a randomised controlled Trial
FITNET	Fatigue In Teenagers on the interNET (Netherlands version of FITNET)
FITNET-NHS	Fatigue In Teenagers on the interNET in the NHS (UK version of FITNET)
GCP	Good Clinical Practice
GET	Graded Exercise Therapy
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology Agency
IMD	Indices of Multiple Deprivation
ISRCTN	International Standard Randomised Controlled Trials Number (Registry)
IMP	Investigational Medicinal Product
JLA	James Lind Alliance
LP	Phil Parker Lightning Process®
MAGENTA	Managed Activity Graded Exercise in Teenagers and Pre-Adolescents
MRC	Medical Research Council
MRC-HTMR	Medical Research Council - Hubs for Trials Methodology Research
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NEJM	New England Journal of Medicine
NHS	National Health Service
NICE	National Institute of Health & Care Excellence
NIHR	National Institute of Health Research
NIHR CLAHRC	National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care
PI	Principal Investigator
PIL	Patient Information Leaflet
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PPI	Patient and Public Involvement
PPT	Patient Preference Trial
PSP	PRioRiTy Setting Partnership
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RCADS	Revised Children's Anxiety and Depression Scale questionnaire
SES	Socioeconomic Status
SF-36-PFS	36-Item Short Form Survey-Physical Function Scale
SMC	Specialist medical care (treatment for paediatric CFS/ME)
SMILE	Specialist Medical Intervention and Lightning Evaluation
SSAG	Study Specific Advisory Group
JAMA	The Journal of the American Medical Association
TMG	Trial management group
TSC	Trial Steering Committee

Chapter 1: **Background – Randomised controlled trials, recruitment and treatment preference**

1.1 Overview of Chapter

This chapter includes a comprehensive review of the key research areas relevant to this thesis, and acts as a backdrop to the area under investigation - treatment preference in paediatric RCTs. Paediatric RCTs are more complex than adult RCTs in terms of communication, consent and perhaps recruitment and retention, since the views and experiences of parents and young people need to be considered before making the decision to participate. In addition to treatment preference and equipoise, which are the areas of primary importance to this thesis, several other methodological and contextual issues are also discussed. These include an overview of: the history of RCTs, facilitators and barriers to RCT recruitment and retention, young people, and parents' motivations for participating in RCT research, ethical issues and the assent/consent process, and finally, communication and decision-making.

1.2 Randomised controlled trials and evidence-based medicine

Evidence-based medicine uses numerous different research approaches and techniques to gather and analyse data to improve health outcomes for patient populations. The randomised controlled trial (RCT) is one such method, and the modern-day RCT is defined by the Cochrane community glossary as:

> *'An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).'* [2]

The hierarchy of evidence (Figure 1:1) has been used to distinguish between the levels of bias (risk of error) that a research method is open to when reporting results from interventions investigating evidence-based medicine and practice, [3, 4] [5, 6]

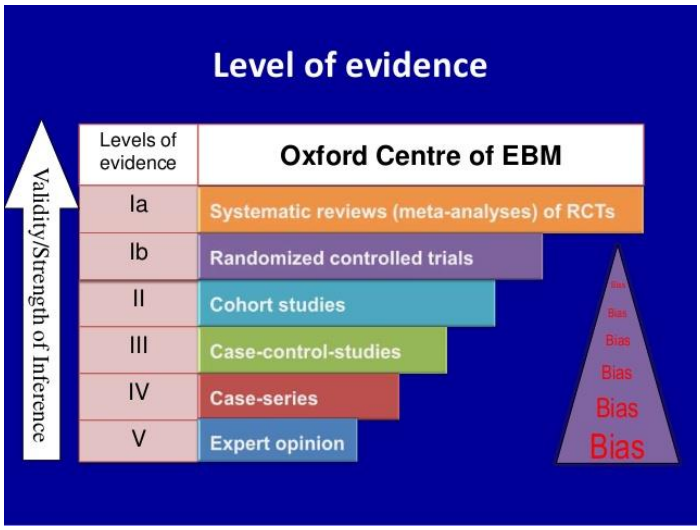


Figure 1:1 The hierarchy of evidence

[3]

Systematic reviews and meta analyses bringing together data from numerous RCTs are the most reliable sources of evidence, for establishing an evidence-base for new medicines, treatments and interventions that might benefit patients and advance medical science. Cochrane Collaboration systematic reviews and meta-analyses sit at the top of the hierarchy of evidence, followed by RCTs. [7, 8] Efficacy RCTs investigate the performance of interventions under 'ideal' conditions, are highly controlled, and have strict inclusion and exclusion criteria. Efficacy RCTs often use a placebo as a comparator and are double blinded. [9] In contrast, 'pragmatic' (effectiveness) RCTs are those which incorporate key elements of real-life routine clinical practice, whilst applying the rigour of randomisation, (distributing known and unknown confounders between groups). [10, 11] Pragmatic RCTs strive to incorporate a wide range of the clinical populations using an intervention, in a setting such as the NHS. Well-conducted pragmatic RCTs enable health-professionals to evaluate the effectiveness of interventions when there is a lack of evidence base in a clinical setting and might compare a new intervention with 'usual' or 'routine' clinical care. [3, 12]

RCT research is not carried out in a vacuum, it is conducted in collaboration with wider multi-disciplinary teams providing health care for the wider population. 2018 marked the 70th anniversary of the National Health Service in the UK. The milestone establishment of the NHS on the 5th July 1948 paved the way for free healthcare for all, with the UK being the first country in the world to provide this to its citizens. Women and children were among the most vulnerable groups in UK society who stood to benefit most from the establishment of the NHS. Prior to its establishment, one in 20 children died before their first birthday, and many women could not afford

to contact a doctor because the vast majority were not in paid employment and ‘national health insurance’ did not extend to female employees, wives or children. [13]

http://news.bbc.co.uk/1/hi/events/nhs_at_50/special_report/123511.stm

https://www.england.nhs.uk/

Subsequent important government white papers, such as The Health of the Nation [14] in 1992 have been pivotal moments in the evolution of the NHS, with a shift in emphasis from ‘sickness’ to the promotion of ‘health’ and the importance of health education. [15] The NHS research and development (R&D) strategy was formally launched in 1991 [16] and this resulted in the establishment of the Health Technology Assessment (HTA) programme, which was set up by the Department of Health in 1993. [17] The National Institute for Clinical Excellence (NICE) was created in 1999, with the aim of assessing clinical evidence and deciding which new treatments should be used by the NHS. [18] NICE has undergone several changes since it was established, initially merging with the Health Development Agency and renamed as the National Institute for Health and Care Excellence following the Health and Social Care Act of 2012. [18] The EU’s 2006 Amendment Regulations [19] specifically stated that EU law would support and ensure ‘medicinal products are researched, developed and authorised to meet the therapeutic needs of children’. [20]

1.3 The history and origin of randomised controlled trials

Some of the earliest accounts of '*controlled comparisons of alternative treatments*' were carried out in the 16th and 17th centuries by Ambroise Pare [21] and Jan Baptista Van Helmont. [22] Van Helmont used the method '*casting a lot'* to ensure that patients were assigned to two equal groups for the treatment of febrile patients with and without bloodletting. Dr James Lind, a naval surgeon, performed the first 'experimental trial' in the 18th century when he observed the symptoms of scurvy in sailors on long voyages. [23] Lind gave 12 sailors different types of 'treatment' in the form of 'drops' two to three times daily, alongside their 'usual' diet. Participants were provided with either: cider, elixir vitriol, vinegar, sea-water, citrus fruit or an electuary (a drug combined with a more palatable substance such as honey). Those provided with citrus fruits recovered fastest. In 1795 the Royal Navy began to provide seamen with lemon juice on long voyages to combat scurvy, and this later led to a vaccination for the disease. [24] This early account demonstrates an awareness of the need to 'control' and 'compare' treatments between participants, but still lacks any formal method in relation to the way in which participants were selected for each treatment group.

At the end of the 19th century Fibiger trialled the use of serum to treat diphtheria, proposing to treat *'every second patient with serum'.* By separating serum and non-serum-treated patients by day of patient admittance Fibiger was able to conduct a *comparison* and identify that more 'non-serum' patients died from the disease. The British Medical Journal cited this as:

> *'the first clinical trial in which random allocation was used and emphasised as a pivotal methodological principle. This pioneering improvement in*

methodology, combined with a large number of patients and rigorous planning, conduct, and reporting, makes the trial a milestone in the history of clinical trials' [25]

During the 1940s a series of small scale 'controlled' investigations of the potential benefits of patulin for the common cold were carried out by the Medical Research Council (MRC) and published in The Lancet. [26, 27] These small-scale investigations produced mixed findings in terms of efficacy, and it was decided that a larger 'multi-centre', 'controlled' trial should take place. The Patulin trial used several important RCT features, which although modified, are still used today in modern RCT design: unbiased allocation, placebo-control and standardisation of recorded symptoms. This early project was innovative and collaborative in nature, despite the investigation concluded that patulin had no beneficial effect in comparison to placebo:

'The MRC trial of patulin, as a possible treatment for the common cold, is an exemplar of researchers, research funders, manufacturers, patients and government working together with a common purpose to pose and answer an important healthcare question. To do this within less than two years seems remarkable today, and is something that everyone currently involved in healthcare research, policy and decision-making would do well to learn from.' [28] Professor Mike Clarke (Director of the Northern Ireland Clinical Trials Unit and Methodology Hub)

The MRC streptomycin trial investigating treatment options for pulmonary tuberculosis is perhaps the most well-known early randomised trial. [29] The trial is questionable by modern-day ethical standards since patients didn't know they were enrolled in a research study. The initial trial found that streptomycin was not effective for long-term treatment of tuberculosis, but it resulted in several subsequent

tuberculosis RCTs and further investigation of drug resistance which eventually resulted in a 100% cure rate for the disease. Previously, around 50% of those who developed the disease died. [30]

Ethical issues and RCT research was being debated in the 1950s, with some academics questioning the ethical implications of withholding potentially effective medication and treatment from those randomised to control, placebo or standard care groups. [31] During the 1940s and 50s RCTs were primarily funded by government agencies, and the use of RCTs to assess manufacturers' claims in relation to drugs marketed for human use was minimal, [32] with many still relying on 'expert opinion' to approve the use of newly available medications such as antibiotics and antipsychotics. [33, 34] A lack of regulation or use of rigorous RCTs to test medication before use with the human population led to the thalidomide scandal during the early 1960s. Thalidomide was given to pregnant women experiencing sleep disturbance or morning sickness and resulted in babies being stillborn or born with malformed limbs. In the USA this led to the introduction of regulations which resulted in 'controlled' investigation of new medications. [35] Similarly in the UK The National Institute for Biological Standards and Control (NIBSC) [36] was established in 1972 and is now part of the Medicines and Healthcare products Regulatory Agency (MHRA). [37] Such bodies ensure that all medicines and medical devices are safe for use, with specific information relating to the testing and authorisation of medicinal products via clinical RCTs.

RCTs have rapidly increased year on year since the mid-20th century, and the location (country) of published RCT research has changed over time, with ‘all other world nations combined’ overtaking the UK and USA in terms of published RCT research in the late 1990s. [38] Although the modern RCT is frequently referred to as the ‘gold standard’ in terms of rigour, the context in which RCTs have been used in modern medicine has raised important ethical and social issues. [39] These became particularly apparent during the 1990s when RCTs were used to investigate treatments for the human immunodeficiency virus (HIV) in developing countries, where it was deemed acceptable to use placebo control groups that would not have been approved as ethical in European countries and North America. [40, 41]

As the number of RCTs have increased, the funding sources of trials has also changed. During the 1960s RCTs were primarily funded by governing bodies or agencies such as the medical research council. However, there is now more reliance on the pharmaceutical and device manufacturing industries for trial funding. This reliance continues to raise questions in relation to conflicts of interest, and the registration of RCTs on nationally recognised trial registry sites, (International Standard Randomised Controlled Trials Number ISRCTN http://www.isrctn.com/), which is now common practice. These sites also encourage those funding RCTs to avoid non-publication of trial findings that do not provide evidence to support their hypotheses (negative trials). [42, 43]

1.3.1 Trial Phases

Modern RCTs can be categorised into ‘phases’ 1-4, (see: Table 1:1) and are sometimes grouped together into early (1-2) and late (3-4) development phases. [44] Early phase trials are usually carried out with adult populations, and only with young people if a disease specifically occurs in childhood/adolescence. [45] Feasibility or pilot RCTs can be carried out during early and late phases but will typically be carried out during phases 3-4. [46, 47]

Table 1:1 Randomised controlled trial phases

Phase	**Overview**
I - First in human	Assess the safety of a drug, device or intervention, including dose-response characteristics in healthy volunteers.
II - Proof of concept/efficacy	Test the efficacy of a drug, device or intervention, e.g., optimal dose in a population of patients with a particular condition.
III-IV - Effectiveness	Involve randomisation, blinding in a patient population. In this phase a new treatment or new way of delivering treatment is compared with a standard treatment. Different doses or different ways of giving a standard treatment(s) may also be compared (or a placebo, if a standard treatment does not exist). An evaluation of the long-term effects of new drugs and treatments over a lengthy period may be carried out to understand more about side effects, safety and long-term risks and benefits. Phase IV trials will only be carried out after the licence for a new drug has been granted.

A feasibility study is defined by the National Institute for Health Research Trials and Studies Coordinating Centre (NETSCC) as '*research done before a main study'* to *'estimate important parameters that are needed to design the main study*'. A feasibility study aims to establish if it is acceptable to carry out a full study and optimise the techniques and interventions that would be used. Typically, the objectives of a feasibility study would include establishing the required sample size, rates of follow-up, the willingness of participants to be randomised and health professionals to recruit participants.

A pilot study is described as being '*focused on the processes of the main study' and 'to ensure that recruitment, randomisation, treatment, and follow-up assessments all run smoothly'.* http://www.netscc.ac.uk/glossary/. A major difference between a feasibility and pilot study is the latter includes a measure of the primary outcome. [47] Pilot studies also have more rigorous methodology (e.g. sample size estimation, randomisation and control group selection) than studies that were defined as 'feasibility studies'. [46] However, a review of published pilot studies from 2007-2008 in seven popular medical journals (Lancet, BMJ, BJS, BJC, BJOG, JAMA and NEJM – see List of Abbreviations) found that most pilot studies reported results as inconclusive, and although the majority stated that a larger main trial would be conducted, very few main trials were located by the authors (nine of a potential 45). [46]

Pilot studies may be stand alone, or internal to the main RCT, i.e. data from the 'internal pilot' phase of a trial can be included in the final analysis of a main trial.

However, there is currently a large variation in the way in which progression criteria, such as recruitment rates or non-adherence to protocol, are used to determine transition to main trial. [48] Avery et al suggest that, instead of simple stop/go criteria, internal pilots should use a traffic light system: ‘go, amend or stop’, allowing trials which may need ‘modification’ in the amber/amend zone to proceed with some degree of caution.

1.3.2 Trial design

Modern RCTs have several key features, some of which have already been mentioned, such as: a *comparison* of two or more interventions, and an explicit method of *randomisation* is used to ensure equivalence of comparator groups resulting in a fair comparison between groups. RCTs also typically involve an evaluation of the effectiveness of the interventions under comparison. RCTs can also be categorised via the way in which the RCT is ‘designed’ or structured. Participants may experience one or more of the interventions offered via groups in the RCT.

Parallel groups

In a parallel group design RCT interventions run in parallel, with different groups of participants experiencing each individual intervention. RCT interventions are assigned *between* individuals in parallel group designs, and parallel RCTs may be fully or partially randomised, whereby some treatment groups include randomised participants, and some include participants who have chosen their intervention. (see: Patient preference trial).

Cross-over groups

RCT interventions are assigned *within* individuals in a cross-over design, which allows the participant to act as their own 'control', thus reducing between-patient variability and allowing a smaller sample size. It is a within-patient design where the participant experiences both interventions available in the RCT, e.g. the participant receives intervention one then 'crosses over' to intervention two (and vice versa). Participants may not receive all interventions in RCTs where there are more than two intervention groups (partial cross-over or incomplete block). Cross-over designs can be used in conditions that are chronic, with relapsing and remitting symptoms such as migraine. There will be a 'wash-out' period between the interventions to minimise carry-over effects.

The N-of-1 RCT design (sometimes referred to as the individualised medication effectiveness tests, IMETs) typically involve multiple cross-over trials involving a single patient. [49-52] The design allows for an examination of therapeutic benefit, and because small patient samples are required, can be of potential value when investigating rare conditions, particularly in paediatric medicine. [53] Patient feedback from N-of-1-trials has been positive, suggesting that participation can provide insight into an illness, and facilitate open discussion between patient and clinician. [54] Combined N-of-1 RCTs can be used to determine which patient groups might benefit most from a particular treatment, and to estimate a population effect. [53]

However, the cross-over design (including N-of-1) has limitations. It can take longer to ‘test’ both treatments in the trial population (N-of-1 design). [49, 55] A cross-over design is not suitable for interventions or treatments that have a sustained effect on the outcomes under investigation, e.g., the first treatment has a residual effect on the second block of treatment. Some conditions and diseases are also not suited to the design: if symptoms are acute, are likely to improve or deteriorate over the course of the RCT, if the disease is likely to be cured during the course of treatment, or result in death before the end of the trial. [56] Cross-over designs can be useful when assessing which treatment ‘outcome’ is preferred by patients or parents, after both have been experienced. But, since there is no randomisation in a cross-over design, the issues associated with patient preferences ‘between’ treatment groups at recruitment to the RCT are not apparent. [57]

Patient Preference Trial

The Patient Preference Trial (PPT) or Comprehensive Cohort Design (CCD) are pragmatic alternatives to the conventional parallel RCT design that uses randomisation to all treatment groups. The PPT is partially randomised, whereby some treatment groups include randomised participants, and some include participants who have chosen their intervention. [58-60] The PPT is an option depending on the nature of the population, condition and trial context, and is often used where preferences for specific treatments are perceived to be a threat to recruitment. [61] The PPT also allows for a comparison between randomised participants (who are presumed not to hold strong preferences) and those that opted to choose a trial intervention who are followed up via non-randomised groups (presumably because of a strongly held preference). However, this design is

problematic due to uncontrolled confounders in the non-randomised trial groups. [62-64]

PPT design may be chosen to investigate a patient population where there is a perceived lack of ‘collective’ equipoise in the patient community. [10] For example, tonsillectomy for recurring and frequent sore throat in children had been a standard medical practice for more than 50 years and trialists anticipated that those in the clinical and patient community would not be in equipoise, preferring surgical over non-surgical management. [65] Trialists used a standard two group RCT design with parallel non-randomised cohort groups, so that parents who declined randomisation could choose a preferred treatment for their child and be followed up via the research protocol. [66]

Comparison of treatment effectiveness in a PPT design will only use data from randomised treatment groups, since a comparison between patients who enter randomised treatment groups and those who choose treatment is unreliable due to unknown confounders. A comparison between randomised and non-randomised treatment groups can be useful to establish whether those accepting randomisation are similar to the wider clinical cohort as treatment progresses. [67] Because the availability of preference groups often results in recruitment to randomised treatment groups being slower, the PPT design can result in increased size and costs because it takes longer to recruit randomised participants. In addition, these trial designs don’t necessarily increase recruitment rates and if there is ‘equipoise’ in the clinical community, and a lack of an evidence base, the PPT does not address or challenge

treatment preferences that may be based on incorrect or misinterpreted information. [68, 69]

Pre-randomisation methods

Pre-randomisation methods such as the Zelen design involve only those randomised to 'experimental' trial groups being informed about trial involvement (Figure 1:2). [70]

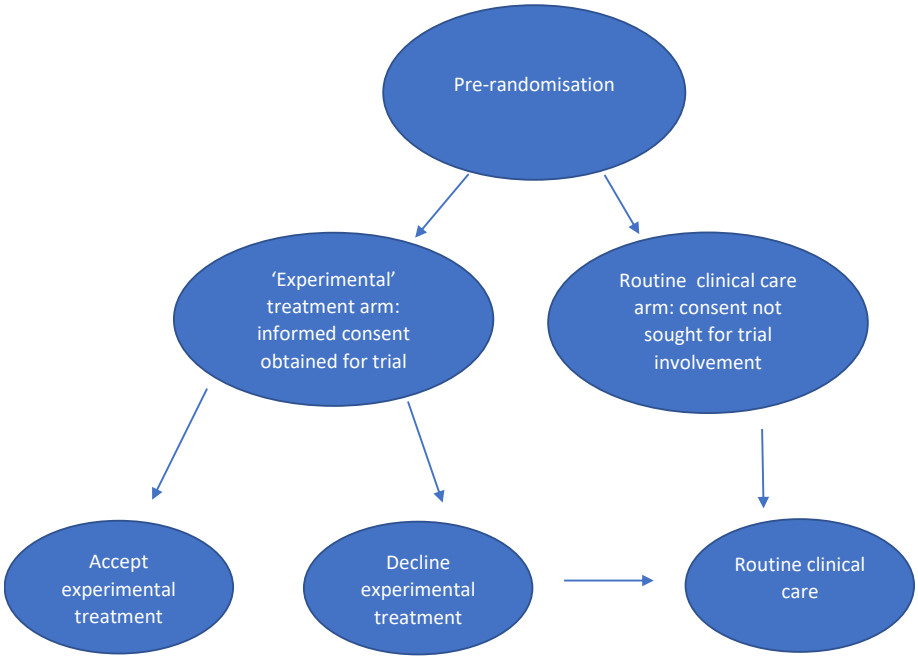


Figure 1:2 Zelen design

This design results in an increase in the rate of accrual, [71] but given the importance of fully informed consent and assent from all those participating in research protocols, this design has significant ethical issues. [72] The Zelen design has been considered justifiable to some trialists and acceptable by some parents in critical care settings, to avoid unnecessary distress for parents of children randomised to 'standard' care groups that might be perceived as less intense or effective than new or 'experimental' treatment offered in a trial. [72-74]

Allocation concealment and blinding

Allocation concealment refers to the method used by trialists to ensure the assignment sequence is concealed prior to random allocation, preventing selection bias. [75] Blinding is sometimes confused with allocation concealment, but blinding occurs post randomisation, and refers to concealment of the intervention or treatment from the participant, i.e. they are not told which intervention they are receiving during the RCT. Participants will typically be provided information in relation to which intervention they received upon trial completion.

Blinding can be used to ensure that participants do not know which intervention they have been allocated. An RCT is described as ‘double blinded’ if treating clinicians or outcome assessors are also unaware of treatment allocation. Statisticians completing analyses are typically unaware of any details of participants’ treatment allocation. [76] Blinding is commonly used in drug trials, or if a trial involves similar interventions. [77] Blinding is not feasible in all RCTs, for example those comparing and evaluating behavioural interventions where participants are asked to follow a specific programme of treatment. [78]

Trials that cannot use blinding are referred to as ‘open’ or ‘open label’ trials. Although non-blinded trials are considered to be ‘at risk’ of bias, [79] recruitment to open trials is 10% higher than blinded trials, i.e., patients like to know which treatment they will receive in an RCT. [80-82] Medical versus surgical management of a condition also poses a problem where blinding and use of a placebo raise additional ethical issues. [83-85] When two surgical procedures are under comparison in an RCT, the

‘expertise-based’ trial design has been proposed as a solution to the fact that surgeons are necessarily unblinded. [86] Participants are randomised to a surgeon with expertise in a specific surgical procedure, thus avoiding problems of differential expertise. This design also aims to address the issue of ‘subconscious’ bias that surgeons may have in relation to a surgical procedure in which they have expertise. Surgeons may be more meticulous while performing a procedure in which they specialise or prescribe co-interventions differently between trial groups.

A survey of surgeons participating in a ‘nailing tibial fractures’ RCT highlighted that surgeons were biased towards one of the procedures under investigation in the trial. [87] Before the RCT commenced, 87% rated the ‘reamed’ procedure as superior. Later in the trial, after 900 patients had been randomised, 86% still rated this procedure as superior with moderate to extreme confidence. Ultimately, trialists must be open and transparent in their discussion of the limitations of unblinded RCTs when reporting and publishing trial findings. [79, 88] Trialists should always strive to ensure that those allocated to different intervention groups are treated as equally as possible in all other respects and ensure that interventions are administered as per protocol, although this is not always the case. [89]

Trial language and terminology

Trialists and patients have varied attitudes towards the use of placebos in blinded RCTs: an adult trial reported that patients did not mind the use of a placebo, but clinicians involved in the study stated this as a reason why *they* were not happy for some patients to be screened for inclusion in the trial. [90] When recruiters were

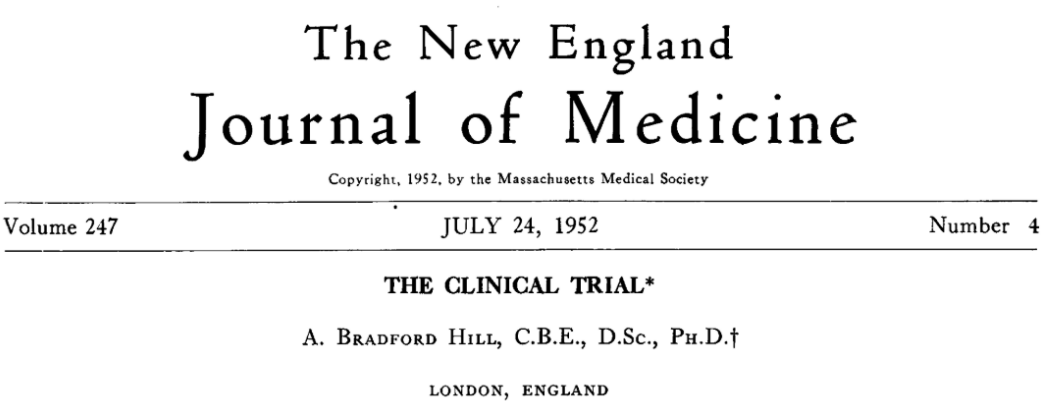
asked to respond to a survey grading facilitators and barriers to recruitment, a large percentage (57%) felt that parent attitudes toward their child taking experimental medicine or placebo were among the most influential barriers to participation. [91, 92] This is also reflected in parent responses to the use of placebo group(s) in RCTs, [92-95] in some cases describing it as ‘dummy medicine’ or ‘no treatment’. [96, 97]

Trial language and the way in which interventions are described can also be a barrier to recruitment. The term “*trial”* can be problematic for some participants and parents. [72] [pg.157] In the ProtecT study some participants viewed a treatment named ‘watchful waiting’ as ‘do-nothing’, ‘no treatment’ or in an extreme case there was the connotation that clinicians would just “*watch while I die”.* [98] [pg.22] This was re-named ‘active monitoring’ to better reflect the way in which patients would be closely monitored. A paediatric trial investigating very low risk Wilms tumour reported lower than expected participation, with parents and clinicians raising concerns that the ‘observation alone’ trial group was not sufficient. [99]

Trial design is diverse, and only designs with issues considered relevant to the research objectives detailed in this thesis have been discussed. This has largely incorporated designs that randomise and recruit at the level of the individual. Ethical issues relating to trial acceptability and preferences for treatment will be substantially different in other trial designs which recruit at the ‘group’ level (cluster, stepped-wedge) or modify parameters as the trial progresses (adaptive platform trials). Therefore, these have not been reviewed. [100, 101]

1.3.3 Randomisation

Historically it was the clinician who decided which treatment or intervention a patient would receive, but in a research context it became apparent that this resulted in group assignment being open to 'bias' e.g., a doctor may assign patients who have been ill for a longer period of time to the 'experimental' group. The 1948 MRC article 'streptomycin treatment of pulmonary tuberculosis', (see: Section 1.3: The history and origin of randomised controlled trials) stated that a '*control scheme'* would be used to determine treatment allocation *'made by reference to a statistical series based on random sampling numbers'.* [29] [pg. 770] Epidemiologist and statistician Professor Austin Bradford Hill used the term *'random allocation of patients',* in an article published by the New England Journal of Medicine in 1952, [102] [pg.115] randomisation in a controlled trial was born:



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THE CLINICAL TRIAL*

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Randomisation equally distributes participants between two or more groups to ensure a fair comparison of trial interventions, using characteristics such as age and gender. Randomisation is typically carried out via a computer-based randomisation program.

Randomisation is generally a poorly understood concept by parents considering trial participation for their child, [103-108] although some studies have found that parents had a basic understanding of randomisation and why it was used: *'that's the thing with the randomisations - they don't have the figures at the moment to say well yes this regime does work better than this regime'*. [109] [pg.6] [96, 110] One reason for parent refusal of 'randomisation' is a wish to have 'decisional control', [111, 112] although parents have retrospectively described randomisation as a process that offered protection from responsibility should their child have a poor outcome. [113]

Misunderstandings about the process of randomisation can lead parents who have made the decision for their child to participate in an RCT to incorrectly believe their child has been allocated a treatment because specific 'factors' about their condition and/or circumstances have been taken into consideration. This is known as therapeutic misconception and can result in the misunderstanding that treatment allocated in an RCT has been 'chosen' because it will specifically benefit the participant. [74, 96, 109, 114-116] Randomisation is also poorly understood by young people participating in RCTs. [105, 117] In a recent study, 10-15 year olds were asked to consider participation in a 'hypothetical' scoliosis RCT involving randomisation to an observation or bracing group. Of those who refused participation, six out of 17 (35%) of the young people with a diagnosis of scoliosis, and 15 out of 28 (54%) without, stated that they would not want their treatment decided by a process of randomisation. [118]

In complex paediatric cancer trials, a staged approach to consent which involved multiple and longer consent consultations was compared with trials using a standard single consultation approach. Multiple consultations were on average 96 minutes long, in comparison to 73 minutes in trials using one consultation. There was an increase in the number of health professionals explaining the concept of randomisation during longer consent consultations. [119] There was also an increase in the number of parents who demonstrated an understanding of the concept of randomisation, although when compared to trials using traditional one-stage consent, neither of these findings reached statistical significance. However, there was a significant difference in the parents' 'trust' scores between the two and one-staged consent consultations. This suggests that well-developed consent protocols that ensure health professionals have adequate time and expertise to provide families with detailed research information in trials should be implemented to improve the process of informed consent. [105, 111, 119, 120] Health professionals have reported discomfort with young people's treatment being selected via a process of randomisation, [121] and concerns about over-burdening families by approaching them about research involvement. [96, 122]

Identifying and exploring preferences for treatment has been one way in which randomisation has been explained and incorporated into the informed consent process by trialists in adult RCTs (see: Section 2.2: Qualitative research and adult randomised controlled trials). [123, 124] Participants are more willing to view randomisation as an acceptable way of making a decision about treatment interventions when they discussed the process with reference to their specific treatment preferences, and when they felt the recruiter was 'truly uncertain' about

RCT intervention options. [125] Discussing the rationale for randomisation, (to remove selection bias or why the trial was being conducted) as opposed to the 'process' of randomisation (that it is carried out by a computer) can provide participants with a better understanding of the reasons why randomisation is used in an RCT setting and improve informed consent. [126, 127]

1.4 Randomised controlled trials research in a paediatric setting

Paediatric clinical care suffers from a lack of good quality randomised clinical trials [128-132] and, since evidence-based medical progress is reliant upon research to find the best treatments for young people experiencing health problems, this poses a challenge for health professionals, researchers, and the wider community. [44, 133-135] Health professionals and policy makers often extrapolate results from adult RCTs, [136-140] and many parents are unaware that the majority of medicines used to treat children and young people have only been tested in adult populations and are prescribed 'off-label'. [141-144] Research with young people can be delayed or not conducted at all for 'ethical' reasons when certain interventions (such as behavioural interventions), are perceived to be inappropriate for investigation with a paediatric population until they have first been rigorously tested in adult trials. [145, 146]

Illnesses that occur in childhood and adolescence can be different to those that occur in adulthood, [147-149] and the way in which young people respond to an illness depends upon their developmental stage amongst other factors such as gender, family adversity or genetics. [150-152] For instance, the rate of recurrence of appendicitis in the paediatric population may be different from the rate in adulthood, since the intra-abdominal inflammatory response is different in children. [153, 154] Young people may respond more positively to certain treatment in comparison to adults, and vice-versa. [139, 150, 155] If we only carry out research in adult populations, many treatments that could potentially be effective for young people may be written off as ineffective, limiting positive health outcomes for children and young people. Conditions such as type two diabetes are now becoming increasingly common in adolescence, and health professionals will be limited in terms of available interventions and medicines if research is not carried out with young people. [156] The fact that children and adults with the same condition respond differently to treatment also has an important implication for the calculation of accurate sample sizes for paediatric populations. [139]

Few clinical decisions involving young people are supported by evidence from good quality clinical trials. In community paediatric practice, only 40% of clinical decisions involving children were evidence-based or supported by good-quality trials, and small sample sizes resulted in RCTs that were less likely to reliably report generalisable treatment effects .[157] Caldwell et al found that parents and paediatricians generally opted for *'the new intervention or standard care rather than trial participation'*. [158] [pg. 804]

Childhood cancer is an area where research with children and young people has been particularly successful in terms of establishing a firm evidence base by enrolling young patients, testing treatments and improving outcomes. The majority of young patients are recruited to trials shortly after diagnosis, [109, 159, 160] and the number of children who survive childhood cancers has doubled from 36% to 76% in the last 40 years. [161, 162] Although clinical outcomes for young people diagnosed with cancer have improved considerably, there is still a lack of older teenagers with cancer enrolling on RCTs. [163-165] Participation in fundraising for cancer research is now largely considered 'the norm' at a wider societal level. There are numerous high-profile commercial advertising campaigns and events held nationally every year. [166, 167]

Research involving young people and their families is becoming increasingly accepted as a 'normal' part of clinical care, with the Nuffield Council on Bioethics publishing a comprehensive report in 2015 which examined the ways in which children and young people could be ethically involved in clinical health research. [44] The report included contributions from more than 500 young people, parents and professionals, [135] and published material in a variety of formats including an online animation accessible to families and professionals:

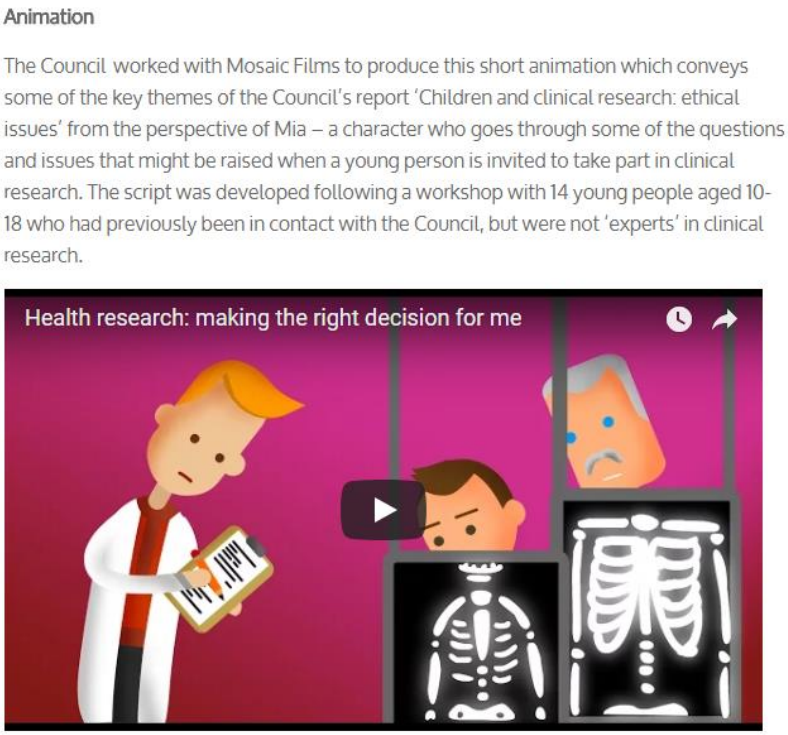


Figure 1:3 Heath research: Making the right decisions

https://www.nuffieldbioethics.org/publications/children-and-clinical-research

In 2016 Nuffield bioethics organisation also issued the 'Statement of aspiration: improving research by involving children and young people', which will be used to inform guidance on good practice and the way in which young people can contribute to research studies in future. [168]

The Nuffield report also supported steps taken by the EU 2006 Paediatric Regulation, [169] but highlighted the fact that there was still much work needed to ensure that young people receive fair access to varied high quality research, specifically in relation to the current waiver system where certain medicines are exempt from the requirement to include children and young people in trials if they are classed as targeting 'adult-only' conditions. [44] [See: Research prioritisation: 53-54

and recommendations 10-11 pg. xxviii- xxix] In a press release in 2015 The Paediatric Committee (PDCO) revoked eight class waivers because new information became available showing that the diseases could occur in children [170] Gamble et al have also pointed out the need for continued revision of the regulations so that they are fit for purposes of deferred consent in paediatric research. [171]

Young people who have participated in RCTs have clearly stated that they believe health professionals should carry out more clinical trials in collaboration with young people. [172, 173] Young people have recommended that results from trials should be fed back to participants as soon as possible. They have also stated that there should be a dedicated secure website where they can show an interest in paediatric trials that are open to recruitment, and network with other young people who had been involved in similar research so that they also have the opportunity to share their experiences. [172]

1.5 Recruitment and retention in randomised controlled trials

Recruitment and retention are of major importance in RCT research. [174-176] Activities that aim to improve recruitment processes can include any activity carried out before participants consent to RCT involvement. [177] Activities that might contribute to improved retention typically occur post recruitment and can be varied. [178] Recruitment problems can delay or prevent trial completion. [124, 179-186]

Sully et al found that 45% of NIHR and MRC trials recruiting between 1994 and 2002 required an extension, with just over half recruiting their originally specified sample size, (55%). [185] More recently, a review of RCTs funded by the NIHR and HTA programmes found wide variability in recruitment and retention rates of RCTs published between 2004 and 2016 but reported a similar figure for trials achieving their originally specified sample size (56%). [187]

Failure to reach the specified sample size and delays in recruitment have also been reported in paediatric RCTs. [184, 188, 189] However, recent findings are more optimistic in relation to the number of paediatric trials that succeed to completion, with only 8.5% reported as discontinuing prematurely. In contrast 10.2% of adult trials and 9.4% of mixed age RCTs (recruiting participants from childhood or adolescence into adulthood e.g. 15-25-years) were discontinued prematurely. [190] Discontinued RCTs are less likely to be published in peer-reviewed journals. [191] A cross-sectional study that compared 173 publications of discontinued RCTs with corresponding details on trial registry sites found that less than half of the published discontinued trials were accurately labelled as such on the corresponding trial registry site. Many discontinued RCTs were labelled as ‘trial completed’, resulting in a lack of accurate evidence for trialists developing future trials. [192] Improving the conduct of RCTs, [174] particularly in relation to the recruitment and retention of participants, can be used to avoid early trial closure and the potential for results to remain unpublished. [175, 193-197] Qualitative research methodology is increasingly being used to improve trial conduct during the pre-trial [182, 198] and feasibility stages of RCTs investigating innovative consenting processes and complex interventions when blinding to treatment is not possible [123, 199-203] and

preferences for treatment may affect recruitment and retention. [78, 123, 204] Qualitative methodology has also been cited as promising in terms of identifying and overcoming barriers to recruitment and retention with paediatric and adult populations. [205, 206]

Fletcher carried out a systematic review of strategies aimed at improving the recruitment activity of clinicians in RCTs. [206] The most successful strategies identified by this review were those using embedded qualitative methodology to design interventions tailored to the individual RCT to improve recruitment, e.g. regular training for recruiters focusing on equipoise, and good practice in relation to research and recruitment methods. [123, 207] However, the QUART (QUAlitative Research in Trials) study found that between 2008-2010 qualitative research was undertaken with only 12% of trials and was infrequent. [208] [209] Research into evidence-based interventions that might be used to improve recruitment by supporting clinical teams recruiting to RCTs is limited. [206] More recently, the Health Research Board Trials Methodology Research Network (HRB-TMRN) and the James Lind Alliance (JLA) formed The PRioRiTy Setting Partnership, (Prioritising Recruitment in Randomised Trials: PSP) to identify unanswered questions about trial recruitment. An online survey yielded 1,693 open-text responses to six questions. The number one question posed by those involved directly in any aspect of RCTs was: ‘How can randomised trials become part of routine care and best utilise current clinical care pathways’. Other relevant trial questions included an analysis of barriers and enablers for healthcare professionals in helping conduct RCTs investigating the best approaches to optimise the informed consent process to improve recruitment. [176]

1.5.1 Factors affecting recruitment and retention in adults randomised controlled trials

Factors that influence recruitment and retention during the implementation phase of RCTs include; trial design, incentives, patient characteristics, support for recruiters, consenting and opt-out strategies. [174, 175, 210-212] Several systematic reviews have been conducted across multiple illness domains investigating trial factors (e.g. participant blinding) and strategies (e.g. telephone reminders) that influence recruitment and retention in adult RCTs. [80, 212, 213] A systematic review of strategies for increasing recruitment to RCTs found that unblinded RCTs had higher consent rates, and increased education about the health problem or disease experienced by participants, as opposed to information provided about trial processes (such as additional audio-visual patient information or a booklet explaining why the RCT was being conducted) increased RCT recruitment. [213]

A comprehensive Cochrane systematic review identifying evidence from 45 RCTs which used a variety of interventions to improve recruitment, was carried out in 2010 and updated in 2018. In the original review, open rather than blinded RCTs, (see: Allocation concealment and blinding') opt-out recruitment, (potential participants are contacted but can decline further contact from the research team) telephone reminders to non-responders and a financial incentive included with the trial invitation were the only interventions which improved recruitment. [212] The updated review included an additional 24 papers, and the only three recruitment strategies which carried a 'GRADE high certainty of evidence' were: open trial design, using telephone reminders and optimising the participant information leaflet. The authors

highlighted that more recently published papers were better reported and judged as more likely to be at low risk of bias.

Limitations of the original and updated Cochrane reviews (and Caldwell review) were highlighted as: the inclusion of 'hypothetical' studies, in which participants were asked to consider how they would feel if they were asked to participate in an RCT. The updated review stated that hypothetical trials would be excluded from future versions of the report because they do not provide findings based on 'real decision making'. [80] [pg. 26] None of the RCTs included in either review recruited paediatric patients, therefore it is not known if the findings are applicable to paediatric trials. The authors highlighted that '*identifying effective interventions to support recruitment to paediatric trials is also a priority'.* [80] [pg. 26] A qualitative Cochrane review is currently under way. This qualitative synthesis will explore factors that impact recruitment to RCTs such as recruiters' perceptions and participants' reasons for declining or accepting RCT participation. There will also be a qualitative evaluation linking the way in which facilitators and barriers to trial participation are addressed by the interventions and strategies already evaluated in the previously published Cochrane reviews. [210]

1.5.2 Factors affecting recruitment and retention in paediatric randomised controlled trials

Literature reporting factors that act as facilitators and barriers to recruitment and retention in paediatric trials can be categorised in the following areas: parent or patient characteristics (which includes characteristics associated with the condition

under investigation), trial characteristics and research or clinical team factors. [92, 172, 188, 205, 214-220]

A recent systematic review cited the parent characteristics - ethnicity, age, education and socioeconomic status (SES) - as the most commonly reported predictive parental characteristics associated with being barriers to recruitment of children to paediatric trials. Older parents who did not identify as being from an ethnic minority group, with higher SES and levels of education, were more likely to consent to their child being involved in RCT research. [205, 214-216] There were similar findings in relation to retention rates, with characteristics such as, unmarried parents/caregivers, low SES and ethnic minority status being predictive of lower treatment completion and rates of retention in randomised [215] and non-randomised [221] clinical research. In contrast, two US-based trials found that parents who declined RCT participation had higher levels of education [218] and SES. [111] A limitation of focusing on parent characteristics in relation to recruitment and retention is the fact that it is unclear whether parents 'perceived' to be from lower SES are not approached to take part in RCT research, either because health professionals think it may be an additional burden, or whether these families are more likely to decline when asked to participate. [222, 223] Parent 'characteristics' that predict poor recruitment and retention do not fully explain the reasons why parents decline or accept randomisation and trial participation for their child.

A variety of factors have been reported to influence parental decision-making in relation to RCT participation for their child. For many parents the timing of

discussions about trial participation and consent is an important factor, [224-226] especially when family members are under considerable stress associated with a new diagnosis. [227] Although some parents will consent to RCTs even when they feel the timing of approach is not ideal, [96] others are more likely to give consent if approached at a less stressful time, such as an out-patient pre-operative setting as opposed to immediately before a surgical-procedure in an in-patient setting. [228]

Other factors that parents have cited as important in terms of being approached about RCT involvement and continued participation have included: establishing a trusting relationship with the recruiting team with honest discussion of risks and benefits of research, [214, 224, 229-232] continuity of care, (speaking to the same person on the trial team at various time points during RCT data collection), and professionalism of the recruiting team. [189] [218] Reassurance about logistical factors, (e.g. the amount of time off work that research participation will involve) and personalised discussions, including additional time spent answering questions are also considered important by parents. [227, 230] Concern around the type of treatment offered in RCTs, e.g. a treatment that is a change from 'current' recommended treatment [225] or when study groups are perceived as very different in terms of effectiveness (placebo versus active treatment), have been cited as issues which make decision-making more problematic for parents, particularly when a child is seriously ill. [97, 218, 233] Factors associated with disparity between treatment groups are linked to a lack of equipoise and preferences for treatment. [227] Extended family may also be involved in decisions about treatment and research involvement for young people, and the extent to which wider family may facilitate or inhibit RCT participation is currently unclear. [234-237]

The importance of gaining assent from young people under the age of 16 years was reported as making a difference to engagement in a recent study that required participants to undergo general anaesthetic for tooth extraction. [189] Other authors have highlighted the importance of young peoples' motivation to take part in RCTs. [214, 224] However, it was parents and researchers – not young people themselves – who reported that motivation was a potential barrier to recruitment and retention. Mobile and Internet based technologies are increasingly recognised as important when engaging and recruiting young people in to RCT research. [238, 239]

A recent systematic review found no association between age of participant and recruitment and retention. [205] However, past research has suggested age can be a factor when young people consider trial participation, diabetes trials have found that older children are more likely to decline RCT involvement using behavioural interventions. [215, 226] Young people who were struggling to manage a chronic condition, [227] and had longer duration of illness, [226] were also less likely to consent to research involving blood glucose monitoring. In contrast others have reported difficulty recruiting and retaining younger children in various RCT and observational studies, (specialities included oncology, gastroenterology, internal medicine, ophthalmology, and pulmonary disease). [216] Evidence suggests that young people pay less attention to the potential harm that research may have on their health than parents or caregivers, [229, 240] with young people focusing more on potential benefits of research participation. However, these findings were based on feedback from healthy young people, or those with an ongoing health conditions who were asked to imagine participating in a hypothetical RCT. Such findings may not be applicable to young people and their parents when making decisions about

the prospect of trial participation in real life situations involving acute illness or ongoing health conditions.

Trial related factors associated with successful recruitment and retention included having a dedicated trial co-ordinator and having a motivated, experienced, well-trained trial team with good communication skills. [188, 224, 225, 241, 242] Factors such as Clinical Trials Unit (CTU) involvement, being an Investigational Medicinal Product (IMP) versus non-IMP RCT, or having a pilot or feasibility stage, were not associated with successful recruitment in a paediatric setting. [92, 188] Practices of 'patient-centeredness' [214][pg7] have been found to facilitate retention, including: alerting families that calls about the research study would be made from a 'withheld' number, getting families to commit to a contact time/date and specifying preferred modes of follow-up contact. [189, 231] Flexibility in accommodating recruitment and data collection outside of 'normal' working hours (weekends and evenings) can also improve recruitment and retention in paediatric trials, particularly if parents and young people are attending full time work, education or college. [189, 224, 238] However, clinical teams have reported burden associated with insufficient staffing levels [231, 243] and time needed to adequately discuss trial participation with parents whilst completing associated research and clinical duties. [214, 242] The availability of dedicated research or practice nurses can be key in terms of reducing clinician burden and facilitating recruitment to paediatric RCTs. [156, 244] Regular monitoring of recruitment figures and frequent opportunities for communication between clinical and research teams can be effective in identifying problems with recruitment and retention early, so that changes to current trial processes can be implemented quickly and effectively. [231, 244]

1.6 Equipoise and uncertainty

Equipoise is uncertainty about which treatment group is most effective, or about the benefits of a new treatment because of the lack of an existing evidence base. [245] The acceptance of equipoise between trial treatment groups is essential for clinicians and researchers recruiting to RCTs. [125, 197, 246-248] Lack of equipoise on a clinical team recruiting to a trial can lead to the early closure of trials in international as well as local settings. [249, 250] However, health professionals and patients will rarely be in a state of 'perfect' equipoise or 'indifference' (absolute uncertainty) before either recruiting to or while participating in an RCT. [251-255] Freedman pointed out that health professionals often have 'a gut feeling' or 'an instinct' about a particular treatment. [251] Freedman also identified the distinction between 'individual' and 'collective' (clinical) equipoise, where team members hold varied 'individual' personal beliefs and experiences of treatments, with their perceived equipoise depending on a number of factors (e.g. length of service, local availability of treatment options or specialty). At the same time there is overall 'collective' uncertainty within a multi-disciplinary clinical team or the expert medical community as a whole. It could be argued that an effectiveness trial would not be funded if there was not a belief (or where possible, preliminary evidence from efficacy trials) that 'new' intervention(s) offered would be more or equally effective. [256, 257]

Many health professionals recruit to RCTs as part of their day-to-day clinical duties. This can be challenging since they are forced to re-frame their every-day clinical experience. In discussions of 'routine care' they might make decisions in relation to which treatment they believe would be most suitable for an 'individual' in their

personal circumstances in collaboration with the patient and their family. [258, 259] During RCT recruitment consultations they must instead approach and frame the discussion by disclosing to the patient/family that there is uncertainty in terms of which treatment might be most effective for ‘eligible’ patients. This will involve the health professional taking on a dual role of ‘clinician’ and ‘medical scientist’ or 'researcher', depending on clinical experience, their comfort with this dual role may vary. [260-262] Accounts from those recruiting to adult trials have highlighted an emotional and intellectual burden associated with reconciling the dual roles, required when recruiting to trials in addition to providing a more traditional clinical consultation. [246]

Theories of equipoise pose an ethical issue, and are problematic when applied to the practice of modern clinical care and evidence-based medicine. [263] There has been debate and discussion about whether ‘true’ equipoise exists in the context of RCTs, where there is conflict between individual patient benefit, [116, 264, 265] and developing an evidence-based treatment for future patients and families. [251-255] Gifford proposed a ‘sliding scale’ approach to equipoise, highlighting that patients and clinicians may be ‘in equipoise’ to different degrees, and at different points in time. There is continued fluctuation in personal and collective (clinical) equipoise. This will change over time at the individual and group level as trials progress. [255] Authors have also incorporated elements of non-exploitation framework to the concept of equipoise. [266-269] This approach considers the associated risk/benefit ratio of participation for participants. Benefit versus risk may be particularly relevant in paediatric research where parents are making decisions on behalf of their child. Parents will be seeking to protect their child from harm, whilst weighing up the

potential opportunity of having the newest treatment available in a trial, (see: Factors affecting recruitment and retention in paediatric randomised controlled trials). [270]

Although ethical debates around equipoise continue, [271, 272] the pragmatic issues which relate to equipoise, including judgements about eligibility criteria, and the way in which equipoise is conveyed and discussed with prospective RCT patients, continue to impact recruitment to RCTs. Those recruiting to RCTs have expressed the view that patients located in the 'middle ground' of the eligibility criteria were more readily perceived to be candidates for an RCT. However, those at either end of the eligibility spectrum had potential to be excluded on 'subjective' grounds based on 'hunches' and 'bias'. [262] Empirical support for this can be found in other paediatric RCTs, [273] [260] and in the wider theoretical literature. [31, 102, 274-277]

Rooshenas drew on evidence from audio-recorded recruitment consultations and interviews with clinicians involved in recruitment to six RCTs, finding that clinicians' personal views about trial treatments influenced the way in which they conveyed equipoise to prospective participants. Practices that compromised the communication of equipoise included: offering treatment recommendations as 'expert opinion', providing imbalanced descriptions of trial treatments (for example, by referring to one treatment as 'traditional') and disclosing 'personal opinions' based on intuition. To what extent this resulted in participants declining trial involvement in the six trials is less clear. [177] There is also some evidence to suggest that doctors and nurses may communicate equipoise differently. Feedback from recruiting nurses suggests that when recruiting to RCTs, their equipoise is influenced by the

practicalities of treatment options, families circumstances and their clinical background. [262] [278]

1.7 Treatment preference and randomised controlled trial research

'Treatment preference' can be described as: *"any favouring or liking, to any degree, towards a particular treatment".* [Mills et al 2014, pg325] [247] It can also be framed as a lack of equipoise in a clinical trial setting. Preference for treatment can affect RCTs in several different ways. [279] If patients have a preference for treatment offered in an RCT they may decline randomisation to access treatment outside the trial. [280] If participants with a preference for treatment consent to randomisation but withdraw from the trial if they don't receive their preferred treatment, this will result in the loss of statistical power to measure differences between treatment groups. [179, 181, 183, 281-283] The external validity of an RCT may be compromised if patients with treatment preferences decline to participate, since trial results will not be representative of the larger population. [63, 91]

Bias is possible if uneven numbers of participants drop-out or cross to the opposite treatment group. This may pose a threat to the internal validity of the trial if large in magnitude. [279, 284] [67, 285] If reduced numbers of eligible patients are recruited or drop-out because of treatment preference this will delay recruitment or prevent trial completion, (see: section 1.5). Strong preferences for surgery were apparent in

a trial of treatments for acute anterior cruciate ligament injury, with many participants stating that they joined the trial to bypass surgical waiting lists. Participants consented to trial participation despite their lack of equipoise, and a high number who were randomised to the non-surgical training group crossed-over to receive surgery (22/34), but these participants did not necessarily report satisfaction with surgical outcomes in terms of recovery. [286]

Preferences for treatment can also affect adherence to treatment groups in RCTs where blinding to trial interventions is not possible. [62, 287-289] If a patient is not in equipoise about treatments offered in a trial but still opts to participate because there is a chance, they may be assigned a preferred treatment, (e.g. in situations where treatment is not accessible outside the RCT) they may suffer ‘resentful demoralisation’. This is a state attributed to participants who have worse outcomes because they are randomised to their non-preferred treatment group. [62, 284, 290] Counter-intuitively, in some cases there is greater compliance to a study protocol by participants who did not get their preferred treatment. [289] This highlights that preference is not straight-forward or static and may change over time or differ between family members (e.g. parent and young person). A trial investigating type-one diabetes in childhood found that although the majority of families expressed a preference for ‘home based’ (as opposed to hospital based) treatment before randomisation, most expressed a preference for the allocated treatment that they had experienced when asked about preference retrospectively (interviews were conducted 15-20 months post diagnosis). [291]

Two systematic reviews have examined treatment preference in RCTs, [279, 289] but findings relating to the effects of preference on recruitment and retention are not straightforward. The first, published in 2005, looked at the effects of participants' and professionals' preferences on recruitment and treatment outcomes. [292] This systematic review extracted data from 34 RCTs, four of which were paediatric, (papers published from 1966 to 2003). It concluded that preferences did influence recruitment to trials, but there was little evidence to suggest that internal and external validity were compromised. Data suggested that refusal of randomisation was based on factors such as: unusual interventions (e.g. acupuncture), where differences in time committed to treatment were required (e.g. outpatient or inpatient treatment) or where treatments differed in terms of desirability (e.g. antidepressants or psychotherapy). [279]

The second systematic review, [289] published in 2008, investigated the influence of preference on attrition and outcome (the RCTs included in final analysis were all in the area of musculoskeletal medicine). This review identified 17 patient preference RCTs and extracted data from 11, none of which were paediatric (papers published from 1999 to 2013). It found that participants who received their preferred trial group had better treatment outcomes. Treatment preferences were not detrimental to attrition rates, and participants randomised to their non-preferred treatment were more likely to return outcome measures.

These systematic reviews did not report reasons for participant preferences qualitatively. Data relating to expressions of treatment preference as a reason for declining or withdrawing from paediatric RCTs has not been systematically reviewed

to date (see: Chapter 4). We do not therefore know whether preference is an important factor when parents and their children consider trial participation.

Since paediatric trials involve the combined preferences of parent(s), patient and health professionals, in addition to a more complex consent process, the issues that pose as barriers or facilitators to recruitment in paediatric trials may differ from those cited in adult trials. [96, 107, 113] Preference for treatment may also influence retention differently in paediatric trials since there is the potential for parent and child to have different preferences or different 'strength' of preference in relation to allocated treatment. Identifying relevant paediatric RCT papers that have reported treatment preference as an issue in terms of recruitment or retention is challenging, (see: Chapter 4: Implications for future systematic reviews in this area). However, the recently developed ORRCA project (Online resource for Recruitment Research in Clinical triAls) has categorised papers into 'recruitment research domains', with the aim of helping those involved in trials research to identify and locate papers of interest and relevance to their area of research (e.g. Patient/Clinician preference). To date, *'relatively few studies addressing recruitment of children under 16 years (12%) or aged between 16 and 18 years (7%)'* [293] [pg4] have been indexed via ORRCA, but going forward this is a valuable online resource with promising potential.

Due to the complex nature of preference development and maintenance in RCT research, the 2005 systematic review of empirical preference literature [279] was accompanied by a conceptual framework that focused on the nature of preference and the development of a conceptual model that described '*the development and*

operation of preferences'. [294] [pg. 686] Bower et al proposed a four-stage model of preferences, which described preference development and operation, (see: Figure 1:4). [294] In the model, preference is described as an 'evaluation' of the desirability (or utility) of two or more interventions. The first stage of the model focuses on *information* about interventions offered in the RCT. Information may be in the form of patient information leaflets, or wider sources such as the Internet or information conveyed by expert clinicians in the clinical field. The second stage focuses on the *processes* that underly the *judgements* made in relation to the desirability in the interventions. The third stage is a *global preference* for an intervention, and the fourth stage is *patient decision-making about randomisation.* [pg. 687]

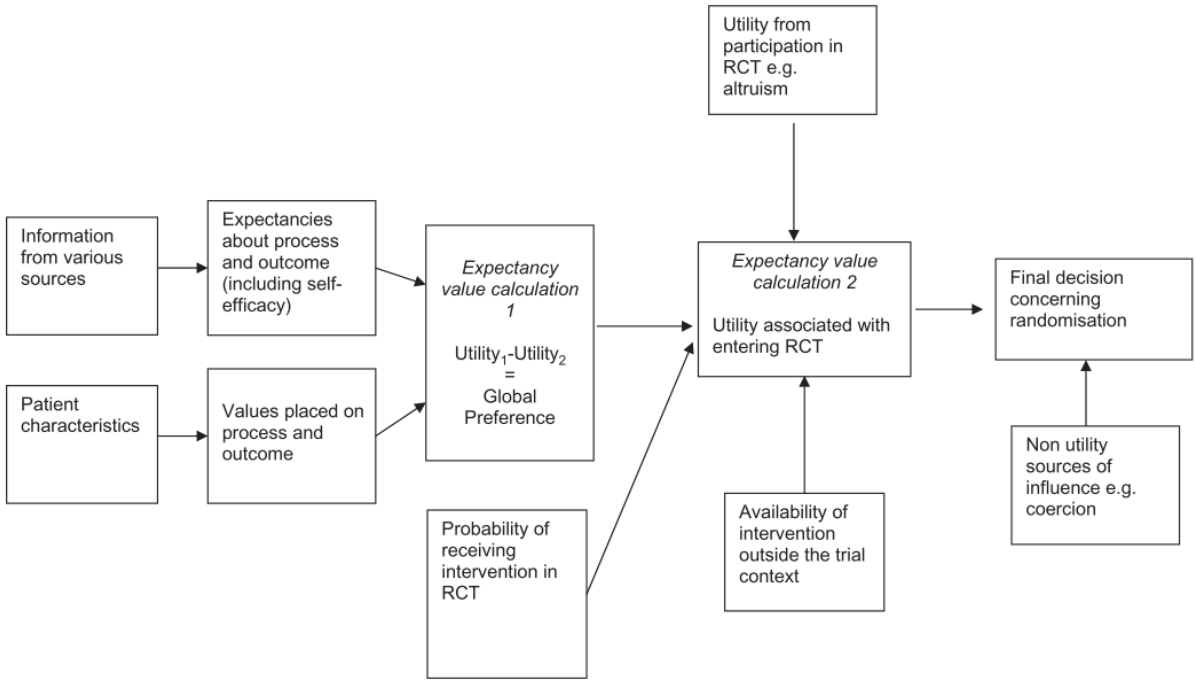


Figure 1:4 A model of patient preference and decision-making

Bower, King, Nazareth, Lampe and Sibbald 2005 [294] [pg. 689]

This is a useful model because it highlights the complexity of preference in the context of RCT research. Preference for treatment is not a simple judgement about an intervention, but incorporates patient characteristics, values and information about the intervention, which may come from a variety of sources. Preferences associated with certain values may be less amenable to change via information provision e.g. those associated with religious belief. Preference judgements also rely on expectancies about outcome that draw on a patient's evaluation of their own self-efficacy. [295]

Self-efficacy is particularly important in the context of trial interventions investigating behavioural interventions, where participants may feel less able to carry out certain 'required' activities, such as physical activity, because of their health condition. Judgements about the utility of taking part in an RCT will encompass not only the benefits of trial participation (such as positive feelings derived from altruistic behaviour), but also the potential benefit of improved health and quicker recovery (which may be enhanced when participants feel they are receiving a 'new' intervention) and opposing judgements about risk (such as intervention side effects). A patient's attitudes toward risk can also play a part in their decision to participate. They may have different perceptions of the level of risk associated with interventions in the RCT. Bower et al summarise:

> *the relationships between expectancies, values and preferences are complex, and there are a number of cases where simple distinctions between 'informed' and 'uninformed' preferences are unhelpful. It may make more sense to distinguish 'informed expectancies', where there is evidence that patients have received sufficient information, clear*

inaccuracies have been corrected, and patients have had time to consider this information in order to make a judgement based on their expectancies and the values they place on them. [294]

Although preference for treatment can influence a patient's decision to accept or reject randomisation as a means of deciding on a course of treatment, in many circumstances preference alone does not determine the acceptance of randomisation and trial participation. There are instances of patients entering a trial despite having preferences for only one of the interventions offered in the trial. [296] If an intervention is not available outside of an RCT problems may arise if patients enter the RCT to access a specific intervention, but then suffer 'resentful demoralisation' when randomised to their non-preferred intervention and either drop-out post randomisation or do not engage with their allocated intervention. [62, 67, 290, 297]

Individual studies that have reported treatment preference in paediatric trials have raised issues relating to parental perceptions of 'experimental' or 'new' treatment as superior to a 'control' group acting as both a barrier and facilitator to paediatric trial recruitment, depending on the trial settings and paediatric condition under investigation. [94] [74] Experimental or new treatments have been reported as more acceptable in RCT setting where parents perceive trial participation as the best route for survival of their critically ill child. In RCT contexts where new and experimental treatments may be perceived by parents as 'riskier' preference for treatment may be a more salient issue. [92-95]

Paediatric trials have the added complexity of multiple opinions about trial participation and preference for treatment, since parents' preferences for a particular treatment may differ from those of their child, [66, 204] just as perception of symptoms has been shown to differ between parent and child in clinical practice. [298] A young person's developmental stage, age and diagnosis will influence their interaction in the recruitment consultation, and a family's decision to participate in a paediatric trial. [97, 299-301] A recent RCT recruiting adolescents to an obesity treatment trial found that a common reason for non-participation was adolescent refusal to participate, despite their parent giving consent for them to take part. [302] This highlights the fact that parent and child views on participation must be considered in parallel during paediatric recruitment consultations.

Health professionals may have preferences for their own 'specialty' (e.g. surgery) whilst recruiting to a trial which involves surgery as only one trial option in addition to other specialties such as chemotherapy or active monitoring. [246] Evidence from comprehensive cohort studies with randomised and non-randomised treatment groups suggests that health professionals were '*the dominant factor in choice of treatment among non-randomised patients*'. [279] [pg45] In both adult and paediatric trials, the extent to which recruiting health professionals were in equipoise has been shown to influence recruitment. In some cases, eligible patients are not entered into the trial because recruiters have a 'hunch' about a specific treatment or feel that certain groups of patients are 'better suited' to particular treatments because of characteristics such as age or symptom severity. [303, 304] [305] Recruiters have indicated that they find approaching parents about paediatric trials problematic, because they wished to avoid over-burdening families. [96, 122] In contrast, parents

who had been approached about trials reported that they did not find this burdensome, but felt it was a positive and exciting opportunity. [94, 96, 121, 306]

1.8 What motivates young people and their parents to take part in RCTs?

For some, treatment preference for an intervention might be a motivating factor for trial participation. [66] Two motivating factors reported by young people when considering trial participation include perceived personal health benefits [117, 172, 307-310] and altruism. [172, 216, 307, 311] Access to treatments or medical equipment which might otherwise be unavailable, [309, 312] a better understanding of their condition, closer monitoring and access to a specialist team [172] were all factors which young people considered motivational in terms of benefits to their health situation. Some younger children (aged 9-13 years) have been found to misunderstand RCT treatment to mean ‘individualised’ treatment which would directly benefit them, highlighting that extra care should be taken to avoid therapeutic misconception with younger patients when explaining RCT research. [216] Altruistic motivations for participation included elements of helping future patients and giving something back to the health-care teams caring for them. This has been described as a ‘network of exchange’ whereby trial participation was described by young people as a way of giving back to society, future patients, friends and relatives. [172]

Financial reward was cited by some young people as an incentive for taking part. [172, 311-313] Those who discussed financial incentives stated that this showed an appreciation for their participation, but some said they would still have taken part in the trial had this not been offered. [172] Some young people suggested that this type of incentive could encourage young people to take part for the wrong reasons. [172, 312, 313]

Barriers to research participation have included perceptions of research participation being inconvenient [311] and having competing activities which take priority. [308] Medical interventions such as blood or urine samples and medical examination have also been described as a reason for research dissent. [314] However, those who gave medical interventions as a barrier to participation were a sample of healthy young people. It is less clear how influential this would be for young people with specific health conditions who may have already been required to undergo medical procedures such as blood samples as part of their ongoing care.

The two main motivating factors reported by parents considering trial participation for their child were the same as those reported by young people: hope that their child would benefit directly in terms of specific health outcomes [94, 270, 307, 308, 310, 315-320] and altruistic reasons for participation, which in addition to helping children in future also included a sense of moral obligation and citizenship. [94, 96, 109, 113, 228, 317, 319-330] Parents have reported that they would like to find out more about their child's condition, [93, 319] and that having direct access to a specialist team providing a coherent treatment regime was motivational. [327]

Gaining access to treatment that might not be available (in some cases for free) outside of the RCT was also a factor for some parents. [93, 120] Free treatment is particularly important to those on low incomes in the USA and developing countries, [270, 316, 331] where parents consider research participation as a way to access new and potentially unaffordable health technology or treatments. Other more basic 'incentives' only offered in the trial - including soap, transport and iron tablets - were also mentioned. [270, 316, 331] Parents of children with chronic health conditions such as diabetes reported being more willing for their child to participate if they '*didn't have to change much of anything'* in relation to family life and their child's daily routine. [270] [pg.147]

Ultimately parents want to improve their child's health outcomes, whilst protecting them from harm. For parents the benefits of RCT participation must outweigh any perceived risks posed by taking part. [97, 326, 332] Barriers to participation included inconvenience, [330] parental worries about risky or painful procedures, (such as extra intravenous lines or non-routine blood samples) [121, 321, 330] and, for parents of children with long-term health conditions, not wanting to disrupt the way in which their child had been managing their illness (e.g. metabolic control). [270]

1.9 Ethical issues & randomised controlled trial participation

1.9.1 Medical research and human participants

The declaration of Helsinki is a statement of ethical principles which safeguards all human participants involved in medical research. This acts as a guiding document for those working in medical research. [333] The declaration has been amended since 1964 on a number of occasions, more recently the '*dual role of the physician-researcher*' is acknowledged, with the *'role of healer taking precedence over that of scientist'.* [334] Other authors go further, suggesting that the next revision of the declaration should include a statement about equipoise and uncertainty, which are key concepts at the heart of RCT research. [335, 336] The declaration of Helsinki states that any treatments offered to control participants should be *'the current best standard treatment'*, and that any new treatments under investigation should be *'similarly effective or better'.* [333] In the research community there is widespread evidence that well-designed and conducted RCTs offer patients the best current treatment. [158, 337] The Convention on the Rights of the Child, in accordance with article 49, states:

> ***'****Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services' [338] [Article 24]*
>
> *http://www.ohchr.org/EN/ProfessionalInterest/Pages/CRC.aspx*

Research with paediatric and adolescent populations has been recognised legally and socially as a necessary and positive way in which children and young people can participate in the production of progressive health treatment and policies. [44, 168] Those under the age of 18 are typically identified as a ‘vulnerable’ group in society, who require protection by the law from potential exploitation. [338] However, applying a ‘blanket’ approach which presumes the vulnerability of young people in the context of health care research has also been challenged as simplistic and unethical. A blanket can promote complacency and a lack of progressive ethical research which seeks to improve the evidence-base and care of young people using the healthcare system. [44] Young people who participated in a stakeholders meeting which discussed the concept of vulnerability stated that ‘being prepared’ or ‘being empowered’ were important ways in which health professionals and researchers could address and challenge vulnerability in the context of research, in partnership with young people and their families. [339]

Thinking about young people and their parents as active ‘users’ of the NHS also highlights the importance of ethical research carried out in ‘partnership’ with young people and their parents. With the support of their parents there is no reason to assume that young people are more vulnerable than an adult patient who is given the necessary support to consider participation in clinical research, providing that the research context enables health professionals and researchers to support young people and parents in their decision to participate. This might involve providing interactive, age-appropriate information material such as video or YouTube clips in addition to written patient information leaflets. Giving families the appropriate time and support needed to make an informed decision about research participation is

also an important factor which should be considered. In some cases, treatment and the opportunity to participate in a research study may be time dependent, [340] and young people may be temporarily unable to make an informed decision about participation because they are severely unwell. [341]

1.9.2 Informed assent and consent in RCT research: Children, young people and their parent(s)

Consent for medical research is viewed as an informed decision made by an individual, and acts as a 'voluntary agreement' for their involvement in research. Only those aged 16 years or over are legally able to provide consent to be involved in RCT research. Young people under the age of 16 are encouraged, where possible, to provide their 'assent' for research participation while their parent or guardian would be required to provide legal consent for their involvement. Principles of Good Clinical Practice (GCP) [342] state that 'informed' consent involves an open two-way conversation with a potential participant. Assent refers to the agreement of children under the age of 16 years, who are viewed as 'minors' and are not able to legally consent to be involved in a research study themselves. However, if young people (and children) under the age of 16 years are considered to have the capacity to understand what is involved in taking part in a research study, The Nuffield Council on Bioethics suggest obtaining consent:

> *'We take the view that, where children and young people have this level of understanding, professionals have an ethical obligation actively to seek their consent, not their 'assent', regardless of any additional requirements of national legislation' [44] (paragraph 6.5).*

In a paediatric research setting, young people are usually approached to gain consent or assent to participate in clinical research, alongside members of their immediate family. In most cases this would be the child's mother, father or legal-authorised proxy. [44] Guidelines suggest that young people value being involved in the decision making process about their participation in research. [1, 44] In an RCT context there are four components of informed consent: competence, information, understanding and voluntariness, all of which can also be applied to the process of gaining assent. [343]

Competence

Assent is taken as: 'an expression of approval or agreement on their behalf' and, rather than thinking about assent as a legal responsibility, it can be viewed instead as an ethical responsibility which might empower a child (aged 15 years or under) at a typically stressful and challenging time in terms of their health and wellbeing. [344-347]

Young people aged 16 and over are legally able to provide consent to participate in research, since they are considered to have the intellectual capacity and maturity to make decisions about research participation. Consent from 16 to 17-year olds would usually be supported by a family member. In most cases a parent will also be asked to provide consent for their child's participation, if the young person feels that this is appropriate, and if their parent was present at the recruitment consultation. [347-350] Young people up to the age of 18-years have reported that they are influenced by their parents' wishes when considering research participation, but influence

decreased as their child's age increased. [351] Young people also value being given the opportunity to make their own informed decision in collaboration with parents. [117] Young patients with a chronic or acute condition are typically supported by their parents. [233, 352]

Parent(s) (or a legal guardian) not only support their child through the assent and consent process when they participate in research, but also provide emotional and practical support throughout the course of their child's involvement with a research study. [353-356] In many cases, information is also sought directly from parent(s) when their child is involved in a research study. This might include impact on employment, health resource use, or the wider financial and emotional impact the condition has on parents. In these situations, it would also be necessary to gain parents' independent consent, so that they are able to legally contribute information for use and storage by the research team. [357-360]

Understanding

Since young people develop and mature at different rates (both emotional and cognitive), age cannot be used in isolation to gauge their ability to make collaborative or independent decisions about their health choices and involvement in research. [117, 346, 361-365] For this reason, those recruiting into paediatric RCTs must make case-by-case decisions about the extent to which they involve children and young people in the decision-making process in collaborative discussions with parent(s). Assent has been described as 'the emergent capacity to agree' in a very young child, to a 'knowing agreement' in an older adolescent who is able to make a decision

about participation but does not yet have the legal capacity to provide consent. [44] In some instances children and young people may not have the capacity to be involved in a discussion about research participation because their diagnosed condition or health related circumstances do not allow this (e.g. they are severely ill or unconscious). [366] In these circumstances, and where research involves very young children and babies, parents or the child's legal-authorised proxy would be involved in discussions with health professionals, to establish whether or not research participation is the way in which the family wish to proceed. [367]

Information

Young people and their parents will be provided with specific, and usually separate patient information leaflets (PILs) informing them about a research study or RCT for which they are eligible to participate. [345] A PIL may be provided before or after a discussion with a health care professional. These discussions are often referred to as 'recruitment consultations', and the language used by health professionals should be pitched at an appropriate level depending on a young person's developmental needs, without the use of unexplained medical jargon or research terminology. Situational factors should also be taken into account, such as the timing of the approach [119, 368] and if the child's condition allows, actively engaging with both the young person and their parent(s). Parents may feel particularly vulnerable when approached about a research study due to the circumstances that surround their child's illness, and this should be considered by those discussing research studies with families. Ensuring that all involved in the discussion feel comfortable about raising their own specific questions or concerns about a research study is an important part of the informed consent process, which may require more than one

consultation and a ‘cooling off period’ for the family to consider the information they have discussed. [189, 369, 370] Further research is needed to investigate how best to communicate information about trials to families in varied and challenging paediatric trial environments [107, 113, 200, 306, 371-374]

Voluntariness

Voluntariness is a concept that may be challenging to understand when confronted with an RCT embedded in an ongoing or acute clinical care setting, [375-378] particularly in circumstances where parents and young people may be distressed and vulnerable. [379] However, in some studies children as young as six years of age have demonstrated a basic understanding of the purpose of research. [311, 376] Research involvement, unlike routine medical care cannot be framed as solely for the benefit or best interest of the child. In addition, there should be an understanding that the child’s involvement will contribute to something that will potentially benefit other families and wider society in the future. Research participation may indirectly benefit the child and should pose no additional risk or unacceptable burden to the child. [366]

If a family is presented with trial information by their diagnosing clinician, the line between clinical care and voluntary research involvement may be more blurred than those introduced to a trial by a research nurse or researcher they have never met before. [109, 380-382] Parents may feel a sense of gratitude toward a clinical team providing ongoing and/or lifesaving care for their child, [96] and may not want to disappoint recruiters who have spent time explaining trial information. [325] Young

people have also reported feeling an obligation to take part in research because of perceived pressure from parents and/or those caring for them clinically. [307, 383] However, families (both young people and their parents) have also reported feeling empowered when approached to participate in research, when approached by a health professional they know and trust. [96] It is essential that young people and their parents are aware that they are able to decline or withdraw from a research study without it affecting their continued healthcare. [384] Difficulties may arise when parents and young people (who are the prospective participants) disagree about whether research participation is the best course of action. Although the autonomy of young people should be respected, [385] it is often the parents' final decision that takes precedence and health professionals must be mindful to ensure that discussions lead to a joint decision that satisfies all involved. [375, 386]

1.10 Communication and decision-making in paediatric recruitment consultations

A young person's age, developmental stage and diagnosis will have an influence on their participation in any joint discussions about consent/assent and their clinical condition (see: Section 1.9.2). [363] Young patients' input in discussions in primary care settings is often limited, with estimates of patient quantifiable verbal involvement in discussions with a health professional in a clinical consultation being as low as 4-14%. [301, 387] Most communication between the clinician and young patient in these discussions was categorised as 'social' talk, or the clinician acting as 'information giver', with the young person having little or no involvement in

discussions about planning and decision-making. [388-390] Most communication in routine clinical care and out-patient consultations takes place between the clinician and the parent(s). [391-393]

Since consent and assent is sought from a parent and young person (where appropriate) for paediatric trial participation, the dynamic of the 'clinician-patient' relationship changes from a dyadic consultation to one that involves one or in some cases two parents, in addition to the clinician and patient. This brings with it added complexity in terms of whether it is the patient or parent(s) who contribute to discussions about diagnosis, planning treatment and research involvement. [394-396] Parental verbal input in research consultations is on average 16%, ranging between 1-49%. [96] Estimates of young peoples' involvement in research consultations is as low as 1-4.5%, with some young people saying nothing at all. [96] Parents reported that when their child raised questions in recruitment consultations, they were most often directed at the parent not the recruiting clinician. Although recruiting clinicians invited young people and parents to ask questions, they often did so via 'closed' questions which resulted in one-word responses. [96] However, 50% of parents approached about trial participation for their child in two trial contexts (HIV infection n=29, and malignant disease n=42) reported that their child contributed to the final decision about research participation. [349]

Because young patients with a chronic or acute condition are typically supported by their parents, [233, 352] this changes the dynamic of the 'physician-patient' relationship from a dyadic consultation to one that is triadic in nature. This brings

with it added complexity in terms of whether it is the patient or parent who contributes to treatment discussion and planning. [397] One characteristic of these triadic communicative interactions is that patients' input can be limited: patient quantifiable verbal involvement is between 4 and 14%. Most utterances were found to be 'social' talk with the doctor, [301, 387] or the patient was an 'information giver' and had little or no involvement in planning and decision making. [388-390] The current study supports this observation since verbal input from young people was minimal in the vast majority of recruitment consultations. This may in part be due to the nature of the illness under investigation, but patients were affected to varying degrees on a mild to moderately severe continuum, so the illness cannot wholly account for this lack of verbal input from patients.

Findings in relation to young people's comprehension of research-related information - which influences their ability to make informed decisions with the support of parent(s) - is mixed. Some research suggests that children and young people are able to discern that there are risks associated with research participation. [312] Other studies have found that young people (aged between 7-18) had poor understanding of the additional risk associated with clinical research protocols, believing that medicines given as part of research protocols were 'proven' to be the best treatment for their illness. [383]

Young people with cancer, who had been recently diagnosed, found it harder to distinguish between research protocols and routine clinical care in comparison to young people in a diabetes study who had been diagnosed for some time. [311] In

circumstances where young people may not fully comprehend the difference between research and routine clinical care, parents often play a vital supporting role and have reported being aware that certain tests and procedures were only carried out for research purposes. [327] The concept of treatment alternatives can also be difficult for children and young people to understand. This could impact on the way in which young people understand RCT participation and clinical uncertainty (equipoise). [117, 383, 398]

Young people making decisions in a healthcare setting have reported feeling most comfortable with a collaborative approach to decision-making, where they felt supported by parent(s) and health professionals, to make the decision to participate. [232, 395, 399] Young peoples' views vary in relation to the extent they want their parents to take the lead and manage the decision-making process during discussions about their treatment. [232] Policy makers recognise the importance of shared decision-making, (e.g. NICE: The National Shared Decision-Making Collaborative). However, a recent systematic review that aimed to examine interventions promoting shared decision making for young people with a diagnosis of cancer found no eligible studies that met the inclusion criteria, despite searching databases from 1946 to 2012 inclusive. [400] The presence and seriousness of a child's condition will influence how comfortable parents feel about making decisions and discussing certain aspects of their child's ongoing clinical care. [299, 300]

1.11 Chapter summary

In this chapter, I discussed the issues relating to some of the challenges associated with conducting RCTs. Recruitment and retention are of major importance in all trial contexts and can be affected by numerous barriers and facilitating factors, including: trial design, (e.g. blinded versus open) trial treatment interventions, (e.g. behavioural versus medical management), patient (and parent) characteristics, and contextual factors (such as health professional equipoise). Less is known about barriers to recruitment and retention in paediatric RCT settings. Some research investigating decision-making in this RCT setting are based on 'hypothetical' studies, or studies involving healthy participants. Findings may not be relevant to decision-making in RCT settings when young people are acutely or chronically ill. Contextual factors that appear to be of relevance to paediatric RCT context include the relationship that families establish with the recruiting medical team or the amount of time families are given to decide about trial participation. Ethical issues of voluntariness, patient autonomy and informed assent and consent are of paramount importance in the paediatric RCT setting, as they are in that of adults.

A conceptual model that considers interlinking preference related factors that influence the decision-making process, including information, values, expectancies, utility and self-efficacy, highlight the complexity of investigating treatment preferences in an RCT context. Investigating preference in a paediatric trial setting comes with the added challenges of complexity in terms of communicating trial information to both patients, (at varied stages in their cognitive and social development) and parents often in stressful circumstances. Family members (those present during the consultation and wider extended family) may have different

preferences for treatment. Preferences are not static, and the fact that young people and parents' preferences for treatment may change over time has implications for behavioural interventions in particular that require 'buy in' from the patient, parent and treating health professional.

Families motivations for participation in RCTs appear to be centred around perceived personal health benefits as well as altruistic motivations, or a 'network of exchange' as a way of giving back to society, future patients, friends and relatives. Health professionals are likely to have varied degrees of personal equipoise when recruiting participants to RCTs. This may affect their decision to approach families, and the language they use to convey information during recruitment consultations with families. In Chapter 2 the way in which qualitative research methods can be used in RCT settings will be explored in relation to the complexities described and outlined in this chapter. Chapter 2 will also provide details of four paediatric conditions and RCTs that were under investigation during the current PhD thesis.

Chapter 2: **Background - Qualitative research in randomised controlled trials**

2.1 Overview of Chapter

Chapter 2 includes an overview of the way in which qualitative methods can be used effectively to investigate recruitment to RCTs, with a particular focus on exploring preferences for treatment. [401] It also details the key qualitative methods and approaches relevant to this thesis, including: qualitative interviewing (face-to-face, telephone and skype), the practice of audio-recording recruitment consultations, and communication training for those recruiting to RCTs (Section 2.3). Quality and rigour of data collected via qualitative research methods is also reviewed in Section 2.3, (trustworthiness, credibility and transferability). Background information relating to the conditions under investigation, (Section 2.4) and an overview of the four paediatric trials from which data were collected and analysed is included towards the end of this chapter, (Section 2.5) and finally the aims and objectives of this thesis are outlined (Section 2.6), along with Figure 2:3 providing a visual overview of the way in which preferences for treatment were explored to address the thesis aim and objectives.

2.2 Qualitative research and adult randomised controlled trials

The value of qualitative research in RCTs is increasingly recognised as beneficial to RCT design and conduct. [401] The ProtecT (**Pro**state **te**sting for **c**ancer and **T**reatment) study demonstrated that qualitative methodology was an effective way to identify and implement changes to RCT recruitment strategies. [98, 123, 207] The study used qualitative methodology to investigate barriers to recruitment and improve informed consent in a field which had previously failed to successfully recruit to RCTs. [402, 403] The authors even went as far as describing the trial as being embedded within the qualitative research:

'*The ProtecT feasibility study embedded the randomised trial within the qualitative research and followed a sociological iterative approach. Thus, qualitative research methods applied in combination with open minded clinicians and flexible or innovative trial designs may enable even the most difficult evaluative questions to be tackled and have substantial impacts even on apparently routine and uncontroversial trials*.' [123] [pg. 769]

Quality improvement report

Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study

Jenny Donovan, Nicola Mills, Monica Smith, Lucy Brindle, Ann Jacoby, Tim Peters, Stephen Frankel, David Neal, Freddie Hamdy for the Protect Study Group

Differences between the complications of treatments offered in the ProtecT study (radiotherapy, surgery and monitoring) but not in survival rates, coupled with past difficulty to recruit had resulted in an environment where there was considerable mixed opinion in the clinical community with O'Reilly stating: *'a study comparing surgery and radiotherapy is still possible, but it is unlikely ever to be a randomised study'. [pg. 1556]*

Recruiting health professionals in the ProtecT study were trained to use techniques which encouraged an open discussion about treatment options, randomisation and RCT involvement to address issues that emerged from earlier qualitative research within the RCT. Techniques included, re-wording misinterpreted terms such as 'watchful waiting' to 'active monitoring', changing the order that treatment options were presented, an emphasis on the equivalence of different treatments, actively exploring treatment preferences, providing evidence-based counter balancing information, and addressing specific patient concerns about treatment. These techniques improved recruitment from 40% to 70% during the first year of the study, [98] and immediate acceptance of treatment allocation rose from 65% to 81% in the following five years of recruitment. [404]

Exploration of treatment preference proved crucial in allowing eligible patients to make a more informed decision about treatment options, many who presented initially with a treatment preference, found that their preference diminished after a more thorough explanation of all trial treatments and the lack of evidence-based treatment. [125] [405, 406] The ProtecT study highlighted that recruiters could be

trained to elicit and address patient concerns about treatment and preferences, in an open and non-coercive way that enabled those who may not have considered trial participation to do so. [124, 247, 407]

Although the rise in those recruited to the trial could not be solely attributed to the changes initiated via the qualitative intervention during the ProtecT study, similar qualitative interventions that specifically target communication during RCT recruitment have now been used in a number of other RCT settings with similar improvements in the overall process of informed consent. [207, 408] Since many potential participants will present initially with a treatment preference, intuitively it is reasonable to assume that these preferences might diminish after in-depth discussion with a recruiter providing a thorough explanation of each trial intervention and targeted evidence-based information. [405, 409] To incorporate elements of measurable improvements in randomisation rates, authors have developed, refined and adapted this approach with varied degrees of success over the past 20 years, [180, 201, 202] and it is now presented as: The ‘QuinteT Recruitment Intervention’ (QRI). [408]

The QRI is undertaken in two distinct phases which can be integrated at any trial phase, including feasibility, pilot, at the beginning of a main trial, or part way through if the trial is experiencing ongoing recruitment issues. Phase one consists of researchers developing an in-depth understanding of the trial recruitment process to identify and investigate sources of recruitment difficulties. This typically includes an investigation of the patient pathway and eligibility criteria, an evaluation of existing

study documentation (e.g. the patient information leaflet and consent forms), and analyses of audio-recorded recruitment consultations to understand what is said by recruiters and how participants respond to trial information. In-depth interviews can be carried out with members of the Trial Management Group, (TMG) clinical and recruitment staff, and participants eligible for recruitment, and there may also be observations of investigator meetings.

Phase two of the QRI involves feedback of anonymised findings to the Chief Investigator and TMG, identifying factors that appear to be hindering recruitment and developing a plan of action to improve recruitment, such as how to explain randomisation and explore patient treatment preferences. There may be the need to redraft the patient information leaflet (PIL) or change aspects of organisation in clinical centres to stream the patient pathway. Phase two also involves an evaluation of the impact of the plan of action, e.g. recording the number of eligible patients consenting to the trial in comparison to the percentage approached about the RCT across recruiting sites to check if recruitment rates are improving. Interviews may be conducted with recruiters, asking about the acceptability of the QRI plan of action and the changes that have been made. The QRI approach is flexible and some or all elements of the model can be used depending on whether or not the trial is recruiting or retaining participants successfully. [408] QRI techniques have not been applied in paediatric RCTs, and further research is needed to explore treatment preference with young people and parents considering RCT participation.

Another useful approach that incorporates qualitative and quantitative methods in trials research is the ‘Study Within A Trial’ initiative that aims to increase the evidence-base in relation to research into trial processes. (SWAT http://www.methodologyhubs.mrc.ac.uk/resources/swat) [410, 411] SWATs have included investigations which measure the effect of PI site visits on recruitment, [412] alternative ways of providing PIL information [413] and assessing the effect of online versus classroom based training for those obtaining informed consent. [414] The SWAT website is a valuable information source for trialists who may be looking for information in relation to a specific area of trial conduct or design. The SWAT repository also allows for meta-analyses of SWATs as more data is deposited, forming a stronger evidence-base for trials methodological research.

2.3 Using qualitative research methods to investigate treatment preference

Integrated qualitative research methods are well placed to capture and report on the complexity of the trial context. Preference for treatment and recruiter equipoise are complex issues that have been explored in adult trials using qualitative methods. [125, 280, 407, 415, 416] Data collected during the early stages of a feasibility or internal pilot RCT, and the insights and theory developed from it are vital when developing future trial protocols, making decisions about stop-go criteria and improving future trial conduct and design.

2.3.1 Treatment preference: recruitment and continued participation

Evidence for treatment preferences can be obtained via detailed tracking and analyses of RCT screening and recruitment logs. If qualitative methods are being used to investigate recruitment processes during an internal pilot or feasibility RCT, this might be carried out as soon as the trial starts screening and recruiting patients, to monitor recruitment numbers in or across sites. Feedback about any misunderstandings can be used early in the trial to instigate changes to recruitment processes or practice, should this be required. [408] There may be reasons why members of clinical team(s) do not screen eligible patients for inclusion in an RCT, e.g. time constraints or a lack of understanding of eligibility criteria. However, failure to screen eligible patients for inclusion could also indicate that those recruiting have an issue with equipoise and feel that one (or more), of the RCT treatments is not appropriate for some or all eligible patients. Further investigation via interview or informal discussion with staff responsible for screening eligible patients may be required to distinguish between the need to implement further training in relation to understanding the eligibility criteria or to address lack of equipoise in relation to trial interventions. [417]

High numbers of participants dropping out immediately post-randomisation could indicate that families who were not allocated their ‘preferred’ treatment were withdrawing to receive this treatment outside the trial. This might highlight that preference for treatment is not being adequately discussed or understood in recruitment consultations and a need for training in relation to equipoise. Further

investigation of what is said during recruitment consultations could be obtained via the recording and analysis of recruitment consultations between patients and recruiters to determine whether preference is an issue. [123, 177]

Views about continued trial participation (retention) can be analysed using qualitative methods such as interview and the recording of intervention sessions to determine levels of engagement with an allocated treatment regime. [418] Trialists may also want to determine levels of engagement with trial outcome follow-up, (trial questionnaires and outcome measures). [419] In some trials treatment is delivered over a number of weeks or months, and pre-randomisation treatment preferences may influence participant engagement with treatment if they were randomised to their preferred or non-preferred treatment group. Participants who discontinue trial treatments may do so because they feel they are not benefiting from their allocated treatment whether they initially preferred it at the time of randomisation or not. Participants may then wish to receive the opposite treatment offered in the trial (termed cross-over) or a treatment offered outside of the trial (discontinued trial intervention). In addition to discontinuing trial intervention, participants may also want to withdraw from trial follow-up. It is possible for a participant to discontinue trial intervention and withdraw from trial follow up or withdraw from treatment but not trial follow up and vice versa (although the later would result in missing data it might indicate that trial treatments were acceptable to participants but trial follow-up was not).

2.3.2 Qualitative interviewing

The participant interview was the most frequently used qualitative method in the field of RCTs when a mapping review was carried out on journal articles published between 2008-2010. [209] Interviews are usually divided into three broad categories: structured, semi-structured and unstructured. Structured interviews are very similar to questionnaires, and widely used to quantify responses. Interviewees would be expected to provide a yes or no answer to set of pre-determined questions. Structured interviews can be used deductively to test existing theory. In contrast, semi-structured and unstructured interviews are more readily associated with inductive data collection, where data are collected with the aim of generating new interpretations and theories. [420-422]

Interviews can be undertaken to explore the understanding and experiences of individuals who have a 'personal stake' in an event or process under discussion e.g. RCT participation. A researcher will typically use an interview topic guide, aiming to cover several different areas of interest, and providing a degree of structure and consistency across participant interviews. Participants will also be encouraged to raise issues they feel to be relevant and important. Using open questions during semi-structured interviews can facilitate a range of responses, and exploration of issues perceived to be important to the interviewee. [421] Open questions are particularly useful since they avoid a short 'yes/no' response to a question and encourage depth of discussion. [421] This type of inductive data gathering can be useful when researchers are seeking to generate insight or theory, when little is known about a research area.

Meaning will be co-constructed by the interviewer and the interviewee during each interview, and the way in which the interviewee 'makes sense' of the questions will be influenced by the interviewer, who is an active part of the interview process. [423, 424] Qualitative researchers routinely reflect on the interview process, recording contextual and reflexive notes after an interview, and discussing relevant issues with colleagues. These reflections on interview content and process can be drawn upon to inform analysis of the interview and improve the conduct of future interviews (see: Section 3.6.2 for further discussion of reflexivity and the interview process).

The time point at which an interview is conducted can have a significant influence on the type of information that is collected. For example, retrospective interviews which occur sometime after a family has been randomised in an RCT may be problematic if researchers are seeking to gain an in-depth understanding of how young people and their parents' feel about the prospect of randomisation, and their preferences for treatment before randomisation. However, retrospective interviews can be useful when seeking to gain insights relating to families' reflections on the process of randomisation and continued participation after randomisation. Retrospective interviews can also provide insights into the way in which families report changes of preference for treatment as a trial progresses ensuring a discussion about participants' experiences of their allocated intervention can take place. [424, 425]

A series of interviews conducted before and after randomisation, and after delivery of a treatment or intervention, may be appropriate to explore views and experiences

over the course of the trial. [426] There may be some instances where the time-point of interview is restricted by the trial protocol, to post randomisation or post primary outcome measure (e.g. six-month time point). These restrictions may be imposed to avoid researcher interaction with participants, and their engagement in an interview that may influence the way participants think about or engage with randomisation or treatment interventions.

Interviews are also useful when investigating what influences decision-making processes. In RCT research this might include the decisions made by recruiters about which patients were eligible and approached about a trial. [408] Interviewing families who do not provide consent to trials provides insight into their reasons for declining to participate, that may include preferences for treatment. Families who decline a trial may feel they need to provide 'justification' as to why they did not wish to take part. [427] Therefore, these families may be harder to engage in the research process, and care should be taken to introduce the 'interview' as a discussion that is inclusive of all families' experiences irrespective of participation outcome. Joint interviews with a young person and their parent, or two parents might also include discussions or debates about what influenced the 'joint' decision to participate, or decline the RCT.

Interviewing children, young people, parents and health professionals

Ensuring that children and young people are able to provide feedback about the research projects they are asked to participate in is a vital part of the successful implementation of modern evidence-based medicine. [44, 428] Feedback from young

people highlights that they often enjoy taking part in research and feel that it is a way of helping others and learning more about their health condition. [172, 173] Ensuring the methods used to collect data are appropriately chosen to maximise the quality of data obtained is vital in any research setting, but when conducting research with young people additional consideration is needed to ensure they feel comfortable and confident in the research setting. Kvale 2007 described the interview process as '*a professional conversation*' [429] [pg. 14] highlighting the asymmetry in terms of power between the interviewer and the interviewee. This power imbalance is exacerbated when interviewing a young person or child, who may feel a need to convey a 'correct' answer. [430-432] In some circumstances a young person may have been encouraged by their parent to participate in an interview (or a research trial) despite their apprehension about the situation. [433, 434]

Encouraging young people (and children) to talk openly with an individual they have just met can be facilitated by building initial rapport with a parent and their child, and by asking age appropriate unrelated or 'non-research' questions at the beginning of the interview (e.g. favourite animal or holiday destination). [428] Methods of building rapport and ensuring children and young people are comfortable with the interview situation will vary depending on the age and preferences of the interviewee. [44, 435, 436] Setting up basic 'ground rules', (prior to the more formal process of signing the assent/consent form) at the beginning of the interview process can give the young person an idea of what to expect, particularly if they have no experience of taking part in a research interview.[433, 437] By confirming how long the interview is expected to last (particularly if children have a chronic condition such as CFS/ME),

‘topics’ the discussion will cover, and that they can stop at any time or not answer questions without giving a reason may help alleviate any apprehension about the ‘formality’ of the interview setting. [438, 439]

Activities such as colouring and drawing while answering questions may help some young people to engage and interact during an interview; these tasks eliminate the need to maintain eye contact between the interviewer and interviewee and change the ‘focus’ of the interaction. [435] Having an interactive interview schedule that children can annotate is also another way of engaging children as the interview proceeds, potentially enhancing their focus and understanding of the subject matter. [440] Sending a ‘topic guide’ or interview schedule in advance (to any research participant irrespective of age), or explaining what the discussion will involve by telephone prior to the interview are also ways in which researchers can ensure young people are more informed about what the interview will involve. [441]

Young people may request that their parent be present during their interview; this can be helpful since it can be reassuring for them, and parents can provide important contextual information allowing the young person to recall more about a situation or procedure. [437] However, any co-constructed interview setting where more than one participant is contributing will potentially be more challenging for the interviewer. [428] Young people may defer to their parent if they are present, and the interviewer will be required to try and actively encourage the young person to answer questions in their own words and from their perspective. [442] Any differences or

disagreements between the young person and their parent should be dealt with sensitively. It is useful to note any observed dynamics which occur during an interview, such as mum or dad interrupting the young person (or vice versa) when they are trying to give an account of their experiences. [442] If a young person is present while their parent is being interviewed it is necessary to be mindful that the young person will be listening to the questions being asked, which in some cases may be directly about their condition and recovery. [443]

Face-to-face, online (skype) and telephone interviews

Face-to-face interviews are often classed as the 'gold standard' context in which to conduct qualitative research interviews. However, more recently online (skype) and telephone interviews have been used in more research settings. [444-447] Skype and telephone interviews can be useful when interviewing participants who live across a wide geographical area, [448] or where travel to participants' homes may be time consuming and increase research costs. Individuals experiencing painful and chronic symptoms, (such as those associated with CFS/ME) can participate in an interview that they might not otherwise have felt well enough to engage in, without the disruption and formality of a researcher coming to their family home. Young people may feel comfortable being interviewed by someone remotely since they participate in many virtual activities and discussion with peers. [449]

Skype and telephone interviews could be perceived as less asymmetrical in terms of the 'power' inequality between interviewer and interviewee, particularly for young people since it is easier for them to leave the interview situation. [448, 450] If they do

not want to continue to answer questions they could simply switch off the Internet connection or call and terminate the interview more easily than if they were participating in a face-to-face setting. [451] One of the most notable issues with skype interviews can be problems with connectivity, sound quality, and difficulties with rapport if there is a time lag between the interviewee and interviewer. [449, 452] Installing the correct software is something highlighted by parents more so than young people as an additional time consuming 'hassle' associated with a skype discussion. [449] The influence of 'researcher effects' based on participants' perceptions of researcher characteristics such as class, age, gender and ethnicity may also be less apparent during telephone interviews. [453]

Interviews with colleagues

Collecting interview data with colleagues who have previously worked alongside the interviewer can also be challenging, irrespective of mode of interview. This may raise ethical issues of disclosure and confidentiality. Although having existing rapport and familiarity may mean that the dynamic of the interview is one which is relaxed and allows for depth of discussion, neutrality will be required if a colleague participating in an interview has a different stance or perception of events. [454, 455]

2.3.3 Audio-recorded recruitment consultations

The audio recording of recruitment consultations as a method of data collection has been used by several qualitative studies investigating RCT recruitment processes. [123, 177, 456] The recording of recruitment consultations is a useful method of

collecting data to obtain an in-depth understanding of the way in which recruiters describe RCT rationale, design and interventions. [408] It is also possible to gain a greater understanding of the questions that prospective participants have when they are provided with information about RCT participation and an understanding of reasons given for declining or participating in the RCT. [123, 125] If RCT information is not being provided from a position of equipoise further training can be provided for recruiting teams as a whole or tailored to suit the needs of individual recruiters and delivered on a one-to-one basis.

Using a combination of data collection methods, particularly audio-recorded recruitment consultations and interviews with recruiters and families, is useful when the aim of data collection is to gain an in-depth understanding of what is said during the course of a recruitment consultation, as well as the way in which individuals reflect upon and make sense of what was said during the recruitment consultation. [96] Data collected via interviews with health professionals can be used to gain greater understanding of recruiters' experiences and feelings about recruiting to trial but can also include an in-depth discussion of specific recruitment consultations, e.g. a consultation which highlighted best practice, or a discussion that felt problematic to the recruiter. [177]

2.3.4 Providing training for recruiters and wider clinical teams

Training can be a key part of improving trial conduct. [206, 207, 247, 408] Providing feedback in relation to recruitment consultations and gaining feedback from health professionals via interviews is important when exploring recruiters' personal

equipoise. [246]Providing on-going support to deal with both the practical aspects of recruiting (e.g. making changes to the recruitment process so it runs more smoothly and targets are reached), and the ‘emotional’ aspects of recruiting to trials (e.g., dealing with patient disappointment), are also of paramount importance. [197, 457]

2.3.5 Assessing the quality of qualitative research

Trustworthiness, credibility and transferability

Terms such as ‘trustworthiness’, ‘credibility’ and ‘transferability’ are often used when considering the quality and rigour of data collected via qualitative research methods. [420, 458, 459] Such terms are used in place of the established concepts of reliability, validity or generalisability, which are associated with the rigour of quantitative methods. [460] Triangulation is a concept that relates to the trustworthiness of qualitative research findings and is used to enhance the credibility of findings and theory generated by a study. Triangulation can involve multiple researchers, data or theoretical frameworks: two or more researchers analysing the same sample of data, two or more data sources or using more than one theory to explain a phenomenon. [461] Triangulation is largely associated with a realist paradigm since it strives to eliminate subjective bias and relies upon the concept of a ‘superior explanation’. [462] [pg. 1117] A similar useful concept is ‘crystalization’: a practice that uses multiple researchers, varied methods and theoretical frameworks, but the aims for doing so lie in the development of a more in-depth and thorough understanding of the issues under investigation. [463] Transferability of qualitative research findings is ensured by reporting a detailed description of the context, participant, and RCT characteristics, in addition to the qualitative research methods

used to collect and analyse data from an RCT. It is then possible for those working on future RCTs to decide if a piece of research is ‘similar’ to their own RCT context and participant population to decide if the findings are transferable. [464]

2.4 Conditions under investigation in this thesis

2.4.1 Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)

Condition: CFS/ME is characterised by debilitating fatigue that is triggered by minimal activity, unlike everyday fatigue which often improves after sleep. CFS/ME patients typically report unrefreshing sleep, post-exertional malaise, cognitive difficulties, (e.g., problems with concentration and recall) and chronic pain. [465] Children and young people will be diagnosed with CFS/ME only if their symptoms have persisted for more than three months. [465] CFS/ME has a negative impact on quality of life and school attendance, affecting social and emotional development in adolescence. [466-470] On average, children aged 11-16yrs with a diagnosis of CFS/ME missed ≥20% of school, [471] and at some stage over half are bed bound. [472] Between 54–94% of young people and children diagnosed with CFS/ME recover with specialist treatment, unlike the recovery rate in adults who have treatment, which has been reported to be as low as 22%. [473-475]

Treatment: NICE 2007 [465] guidance recommends referral to specialist services and that young people are offered ‘specialist care’ which typically means young

patients (who are not participating in an RCT) are offered a combination of Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET) or activity management (AM) to treat CFS/ME depending on their needs and goals. All young people are routinely offered advice about sleep, and medication use. [465, 476, 477] Treatment aims to convert the 'boom and bust' pattern of activity into a sustainable pattern of gradually increased activity leading to recovery. A typical boom and bust cycle of activity involves doing lots of on a good day (physical, cognitive or emotional) when the young person is feeling relatively 'well' and doing very little or nothing on subsequent bad days. On a bad day the young person may be confined to their bed or the sofa because they had 'crashed' and experienced increased symptoms of fatigue.

Specialist Paediatric CFS/ME Service: Treatment in the SMILE, MAGENTA and FITNET-NHS trials was delivered by a paediatric CFS/ME specialist service. During the SMILE and MAGENTA trials, a diagnosis of CFS/ME was given or confirmed during a face-to-face initial assessment appointment. Follow-up appointments were family-based meetings (lasting one hour), with a health professional working on the team. During the SMILE RCT all follow-up appointments were completed on a face-to-face basis, during the MAGENTA trial families were offered follow-up appointments via Skype if they did not wish to travel to a face-to-face appointment. During the FITNET-NHS trial the initial assessment was conducted via telephone, and a diagnosis was provided if this had not already been established prior to referral to the service (see: Appendix 5: FITNET-NHS: Eligibility assessment). The timing and number of follow-up sessions typically varied depending on individual need, but most young people had three to four follow-up sessions spread over three

to six months. Health professionals working on the specialist team included: clinical psychologists, physiotherapists, occupational therapists and paediatric consultants. The specialist team delivered follow-up treatment based on NICE guidelines. [465] Detailed information leaflets on all aspects of treatment (e.g. sleep hygiene, relaxation) were provided on a website maintained by the Paediatric Specialist CFS/ME Service.

2.4.2 Acute uncomplicated appendicitis

Condition: Acute uncomplicated appendicitis is the most common surgical emergency in children, [478] and commonly occurs in early adolescence. The lifetime incidence of appendicitis is 7-8%. [479] It is characterised by inflammation of the appendix which is a narrow tube which extends from the large intestine, see Figure 2:1. Inflammation and the subsequent infection is thought to be caused by obstruction of the lumen of the appendix, typically caused by faecal matter. [480] Appendicitis is experienced initially as intermittent pain in the lower abdomen, which then travels to the lower right-hand side of the abdomen and become more severe and constant. Pressure and movement can make the pain feel more severe and other symptoms include: nausea, vomiting loss of appetite diarrhoea, constipation and fever.

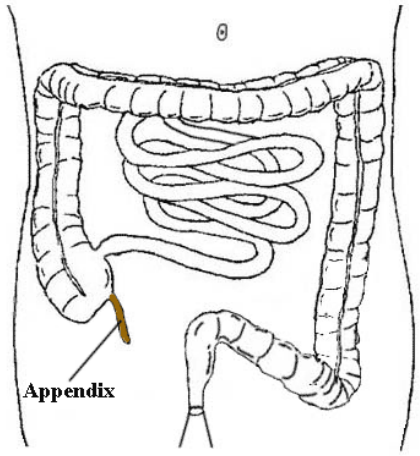


Figure 2:1 Information sheet for teenagers (12-15 yrs.) v2: Inside your tummy

Treatment: In 2014 there were approximately 12,000 emergency appendicectomies performed on children in England. [479] Most surgeons in the UK still consider appendicectomy to be the gold standard treatment for acute uncomplicated appendicitis. [481] Intravenous antibiotics are administered to patients until they undergo an appendectomy either by laparoscopic or open surgery. Although appendectomy is a relatively routine procedure, there are associated risks, which include those associated with a general anaesthetic and the complications associated with surgery. The rate of complications associated with the surgical procedure may be as high as 25%. [482] The need for re-admission to hospital because of post-operative complications is 4-5%. [483, 484] Table 2:1 provides a breakdown of the type of complications which may arise from appendectomy. There is also the possibility of removing a histologically normal appendix. The rate of 'negative' or unnecessary surgery was 10%, when measured in 242 cases of paediatric appendicectomy across 19 surgical units. [485] In the same paediatric population the need for re-admission, re-intervention and complication after surgery was as high as 15%. [485]

A benefit of the removal of the appendix is that there is no risk of a recurrent episode of appendicitis in the future. However, the prospect of undergoing a surgical procedure can cause a significant amount of stress, (both psychological and physiological) for a paediatric patient. Parents are likely to be apprehensive about their child undergoing a general anaesthetic and surgery, and some may question whether a surgical procedure is necessary, particularly if their child presented with few or minor symptoms and begins to recover when given initial non-operative treatment (fluids and antibiotics will be administered prior to surgery). Table 2:1 shows a breakdown of the type of complications which may arise from non-operative treatment of appendicitis. Estimates of recurrence of appendicitis when treated non-operatively in the paediatric population are between 5-25%. [486-488] A recent meta-analysis estimated that the risk of recurrence of appendicitis in 413 children treated non-operatively was approximately 14%. [489] There is a significant financial burden associated with carrying out appendectomy in the paediatric population, this has been estimated to be in excess of 21 million per year. [358]

Table 2:1 Associated risks: Appendectomy and non-operative treatment

Risks associated with surgical (appendectomy) management of appendicitis	**Risks associated with non-operative (conservative) management of appendicitis**
General anaesthetic side effects (common and include: sickness and vomiting, bladder problems, dizziness, bruising, sore throat, shivering or feeling cold and damage to the mouth or teeth) General anaesthetic complications (rare but include: anaphylaxis, waking up during the procedure and death) https://www.nhs.uk/conditions/general-anaesthesia/#complications-and-risks Complications during surgery (damage to other organs and bleeding) Complications after surgery (wound infection, haematoma, intra-abdominal or pelvic abscess, adhesional small bowel obstruction, scarring and incisional hernia) https://www.nhs.uk/conditions/appendicitis/complications/	Antibiotics fail to treat the infection and symptoms to do improve Recurrence of the condition and the need for hospital readmission and further treatment with antibiotics or surgery Adverse reaction to the antibiotics

It has been known for many years that appendicitis can be treated non-operatively, usually in situations or locations where it is not possible to carry out a surgical procedure. [490] There has been a growing interest in investigating non-operative treatment of appendicitis and establishing an evidence base so that it can be incorporated into mainstream health care systems. [491-497] Antibiotics are routinely used to treat complex cases of appendix mass in children and adults. [498-500] In the paediatric population a scheduled or ‘interval’ appendectomy (delayed surgery) had traditionally been performed after an appendix mass had been effectively treated non-operatively.

An appendix mass is the result of a more severely infected appendix, and surgeons will avoid operating immediately because of increased risks of complications and further localised infection. [501] The practice of routinely removing the appendix after successful non-operative treatment of an appendix mass has been questioned in recent years because recurrence of appendicitis is low, and there are additional complications and risks associated with potentially unnecessary surgery. [502] Although data from studies carried out with paediatric patients is scarce, a recent systematic review suggested that 80% of paediatric patients with an appendix mass did not require surgery. [486] A multi-centre RCT carried out with paediatric patients diagnosed with appendix mass also showed that three-quarters could be successfully treated without the need for surgery. [498]

Research into the treatment of acute appendicitis, (which is clinically different to an appendix mass) with antibiotics in paediatric populations has shown that between 62-93% of patients can be treated successfully non-operatively. [503-505] However, these were relatively small studies, and only one used randomisation to allocate participants. [503] Providing it is safe and effective, non-operative treatment for acute uncomplicated appendicitis is considerably more cost effective when compared to operative treatment, The National Appendicectomy Audit showed that 45% of paediatric appendectomies were carried out between 18.00pm-8.00am, therefore non-operative treatment would reduce the demand for costly out-of-hours surgery. [506] Ultimately the safety and efficacy of treating appendicitis non-operatively in children and young people needs to be established via a multi-centre RCT. [358]

Paediatric care for acute uncomplicated appendicitis: Treatment in the CONTRACT RCT was delivered by paediatric surgeons working on three specialist NHS paediatric surgical units in England. This treatment typically consisted of an initial physical examination and diagnosis of acute uncomplicated appendicitis. Young people allocated to receive an appendicectomy underwent either open or laparoscopic appendicectomy at the surgeon's discretion. Young people receiving non-operative antibiotic treatment were cared for by the same consultant surgeons and wider paediatric nursing staff caring for those on the appendectomy pathway (see: Appendix 6: CONTRACT Trial flow).

2.5 Collaborating trials (qualitative data sources)

Table 2:2 Overview of collaborating trials (qualitative data sources)

Scientific title	Acronym	Study design	Condition	Age (yrs.)	REC Reference	ISRCTN Number	Funding
Specialist **M**edical **I**ntervention and **L**ightning **E**valuation	SMILE	Feasibility: Single-centre RCT	CFS/ME	12-17	10/H0202/32 10/H0206/32	81456207	Linbury Trust Ashden Trust
Managed **A**ctivity **G**raded **E**xercise i**n** **T**eenagers and Pre-**A**dolescents	MAGENTA	Feasibility: Multi-centre RCT	CFS/ME	8-17	15/SW/0124	23962803	NIHR
(**F**atigue **I**n **T**eenagers on the inter**NET** in the NHS) compared to activity management to treat CFS/ME in the UK	FITNET-NHS	Internal pilot: Single-centre randomised controlled trial	CFS/ME	11-17	16/SW/0268	18020851	HTA NIHR
CONTRACT: **CON**servative **TR**eatment of **A**ppendicitis in **C**hildren a randomised controlled **T**rial	CONTRACT	Feasibility: Multi-centre RCT	Acute appendicitis	4-15	16/SC/0596	15830435	HTA NIHR

2.5.1 SMILE - Specialist Medical Intervention and Lightning Evaluation

SMILE trial rationale

Many young people accessing the Specialist Paediatric CFS/ME Service have experienced CFS/ME symptoms for a prolonged period of time, [471, 507] and families often enquire about or report using a number of different complementary treatments. These treatments include: homeopathy, acupuncture, dietary methods, herbal remedies and the Lightning Process®. [508] Families accessing paediatric specialist CFS/ME services wanted advice about whether the Lightning Process might be an appropriate treatment for their child, and some provided feedback about their child's attendance on the course. It is estimated that over 250 young people a year used the Lightning Process intervention for CFS/ME in 2010, but no studies had investigated whether it was either effective or safe. [78] Integrated qualitative methodology was used to assess the feasibility and acceptability of conducting the SMILE RCT, specifically to understand issues that would relate to the successful design and implementation of a full-scale RCT (see: Appendix 3: SMILE: Integrated qualitative aims and objectives). [78] The SMILE trial flow diagram can also be found in Appendix 3.

SMILE intervention groups

Specialist Medical Care (SMC) consisted of a combined approach to energy management that included elements of activity management and Graded Exercise Therapy. Young people were routinely given advice in relation to improving their sleep cycle and CBT was available for those who felt they needed additional

emotional and psychological support.

The Lightning Process (LP) course is a training programme which uses the basic premise that the body and mind work together to affect your health. It trains participants to recognise when they are triggering unhelpful physiological responses, with the aim of developing more appropriate responses to challenging behaviours and situations (www.lightningprocess.com). It is run as a group course for 3 hours 45 minutes a day on three consecutive days. Courses were run specifically for young people participating in the SMILE RCT (Appendix 3: Inclusion/exclusion criteria). A parent was able to accompany their child on the course as an observer, they did not participate in course activities. The course is facilitated by one LP Practitioner trained to use principles drawn from neurolinguistic programming (NLP), hypnotherapy and life coaching. Lightning Process practitioners are not medically trained. See Appendix 3: for further details of both SMILE intervention groups.

2.5.2 MAGENTA - Managed Activity Graded Exercise in Teenagers and Pre-Adolescents

MAGENTA trial rationale

NICE guidance recommends that young people are referred to specialist services to receive specialist care which typically involves a combination of either CBT, Graded Exercise Therapy or activity management to treat CFS/ME depending on the patient's individual needs and goals. [465] Since elements of activity management and Graded Exercise Therapy were being used in combination by most of the young people using the specialist service, it was impossible to understand which elements of either approach were resulting in improvements in young people's outcomes.

Treating young people with a combination of Graded Exercise Therapy and activity management also puts significant restrictions on all areas of young people's day-to-day lives (both cognitive and physical activities) and requires them to take in high volumes of information about more than one treatment approach.

During the planning phase of MAGENTA there were several RCTs investigating the effectiveness of Graded Exercise Therapy with adult CFS/ME patients [509] but there was no evidence for its effectiveness or cost effectiveness for paediatric CFS/ME patients. It is not possible to extrapolate results from adult trials, and CFS/ME in young people has been shown to have different symptoms and a more optimistic recovery rate compared to adults. [475] A feasibility trial with young people (see: Appendix 4: Inclusion/exclusion criteria) was needed to assess the feasibility and acceptability of conducting a full-scale RCT investigating Graded Exercise Therapy compared with activity management in a paediatric population, (see: Appendix 4: MAGENTA: Integrated qualitative aims and objectives and trial flow diagram).

MAGENTA intervention groups

Graded Exercise Therapy (GET) is a NICE recommended intervention for young people with mild to moderate CFS/ME. [465] It is currently used by the Specialist Paediatric CFS/ME Service in addition to other CFS/ME treatments such as CBT and activity management. In the MAGENTA trial Graded Exercise Therapy offered advice that was focussed on exercise and a detailed assessment of daily physical activity. Young people were taught how to monitor their heart rate to avoid

overexertion. The level of physical activity was gradually increased in intensity, using a programme tailored to the young person's individual goals. For a detailed overview of the way in which Graded Exercise Therapy was monitored via 'mandatory', 'flexible' and 'prohibited' activities see Appendix 4: MAGENTA Intervention groups.

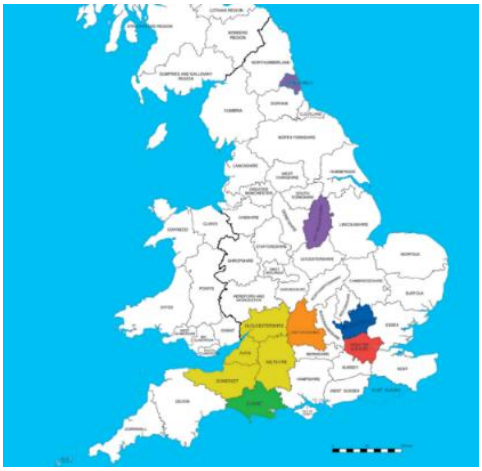
Activity management (AM) is also a NICE recommended intervention for young people with mild to moderate CFS/ME. [465] Activity management is also used alongside other CFS/ME treatments such as CBT and Graded Exercise Therapy. Activity management in the MAGENTA trial focused on the 'cognitive' component of activity management (as opposed to cognitive, physical and emotional components of a combined activity management programme outside the RCT). Cognitive activities that were monitored in the trial included: time at school or doing schoolwork, reading, some craft/hobbies, socialising and screen time (phone, laptop, TV, computer, other devices). For a detailed overview of the way in which activity management was monitored via 'mandatory', 'flexible' and 'prohibited' activities see Appendix 4: MAGENTA Intervention groups.

2.5.3 FITNET-NHS - Fatigue In Teenagers on the interNET in the NHS

FITNET-NHS trial rationale

Most children in the UK are unable to access a local specialist paediatric CFS/ME service (see: Figure 2:2 below). NICE guidelines recommend that children and young people should be offered referral to a specialist service within six months if they are mildly affected, within three months if they are affected moderately, and

immediately if they are severely affected. [465] Because most young people live too far away from specialist services to access face-to-face appointments, having access to online and skype appointments with a specialist team is a potential alternative mode of treatment delivery for patients who often experience an increase in symptoms when they travel a significant distance from their home. Although FITNET was found to be effective in the Netherlands, [510] it has not been used within the NHS in the UK therefore, it was necessary to investigate whether the implementation of FITNET in the NHS is cost-effective, feasible and acceptable (see: Appendix 5: FITNET-NHS: Integrated qualitative aims and objectives and trial flow diagram) to young people, and their families, (Appendix 5: Inclusion/exclusion criteria).



Coloured areas represent specialist paediatric CFS/ME services in UK.

Included in this thesis courtesy of Professor E Crawley.

Figure 2:2 Specialist paediatric CFS/ME services in UK

FITNET-NHS intervention groups

FITNET Online CBT is a treatment package specifically for paediatric CFS/ME patients, it was created in the Netherlands. [510] The programme has psycho-educational and CBT sections for young people and a separate parallel programme for their parents. The psycho-educational sections include information on: the causes

of CFS/ME: the relationship between CFS/ME, anxiety, depression and other illnesses. How the diagnosis is confirmed. Treatment for CFS/ME. How to explain CFS/ME to friends and what the future (without CFS/ME) is likely to look like. The CBT section is activated by a clinical psychologist once the child/parent has completed the psycho-educational sections (Appendix 5: FITNET-NHS Intervention groups).

Activity management via Skype incorporated cognitive, physical and emotional components of a combined activity management programme (unlike the MAGENTA trial which focused only on the cognitive component). During the FITNET-NHS trial treatment all appointments were delivered via skype. For a detailed overview of the way in which activity management was monitored via 'mandatory', 'flexible' and 'prohibited' activities see Appendix 5: FITNET-NHS Intervention groups.

2.5.4 CONTRACT - CONservative TReatment of Appendicitis in Children – randomised controlled Trial (Feasibility study)

CONTRACT trial rationale

The aim of the CONTRACT study was to assess the feasibility and acceptability of recruiting children and young people (see: Appendix 6: Inclusion/exclusion criteria) to a multi-centre RCT with two intervention groups, non-operative (antibiotic) or operative treatment (appendectomy) for acute uncomplicated appendicitis. Antibiotics are routinely used to treat complex cases of appendix mass in children and adults. [498-500] Cases of appendix mass are initially treated with antibiotics to reduce infection, which can include peritonitis and infection of the abdominal cavity lining. After 4-6 weeks of antibiotics patients would then typically undergo an interval

appendectomy (delayed surgery). However, if patients are recovered the question as to the necessity of surgery is raised. Many parents find the proposal that their child needs emergency surgery frightening and one they are keen to avoid if a safe alternative is available. [358, 504] Antibiotic treatment for acute appendicitis was (and is currently) not routinely offered by the NHS when children, young people or adults are given this diagnosis. Findings from the CONTRACT feasibility trial will be used to determine whether families are willing to participate in a trial comparing surgical and antibiotic treatment for acute uncomplicated appendicitis in young people, and whether surgical teams are able and willing to recruit. (see: Appendix 6: CONTRACT: Integrated qualitative aims and objectives and trial flow diagram). This will inform the planning and implementation of a larger full-scale multi-centre cost effectiveness, pragmatic RCT.

CONTRACT intervention groups

Non-operative intervention (antibiotics): Young people randomised to receive antibiotic treatment received fluids and a minimum of 24-hours broad spectrum intravenous antibiotics, (cefotaxime and metronidazole) as per local policies. Reviewing surgeons actively monitored participants for any changes in symptoms, such as (but not limited to) increased fever, tenderness and tachycardia. Formal reviews were performed 24 and 48 hours post-randomisation, and any participant deemed to have significantly deteriorated underwent an appendicectomy. If consultant surgeons observed deterioration at any stage prior to the 24 and 48 hour reviews the possibility of an appendectomy was discussed with parents and the patient where appropriate. All decisions were based on the clinical judgement of the

treating consultant since predefined criteria for the management of non-operative appendicitis did not exist. Participants who were stable or improved clinically continued with antibiotic treatment and active monitoring. Participants who required an appendicectomy for failure of non-operative treatment underwent an operation and were treated post-operatively according to standardised appendectomy treatment pathways at each participating institution (described below).

Operative intervention (appendectomy): Participants randomised to receive an appendectomy received fluids and broad-spectrum intravenous antibiotics from the time of randomisation (identical to those used in the non-operative intervention group). Participants then underwent either open or laparoscopic appendicectomy at the discretion of the supervising surgeon. See Appendix 6: CONTRACT: Intervention groups for further information about both intervention pathways.

2.6 Thesis aim and objectives

Aim:

To explore how treatment preferences influence recruitment and participation in paediatric RCTs.

Objectives:

1. Undertake a systematic literature search and qualitative synthesis of studies that have reported treatment preference in paediatric RCTs, (children and young people aged 0-17 years and parents).

2. To develop an understanding of the way in which treatment preferences are expressed by young people and their parents during recruitment to paediatric RCTs.

3. Understand how health professionals respond to treatment preferences expressed by young people and their parents.

4. Investigate the effectiveness of recruiter training in responding to expressed treatment preferences and explore whether this had an impact on recruitment.

Figure 2:3 (see next page), visually displays the way in which the aim and objectives were approached for write-up in this thesis.

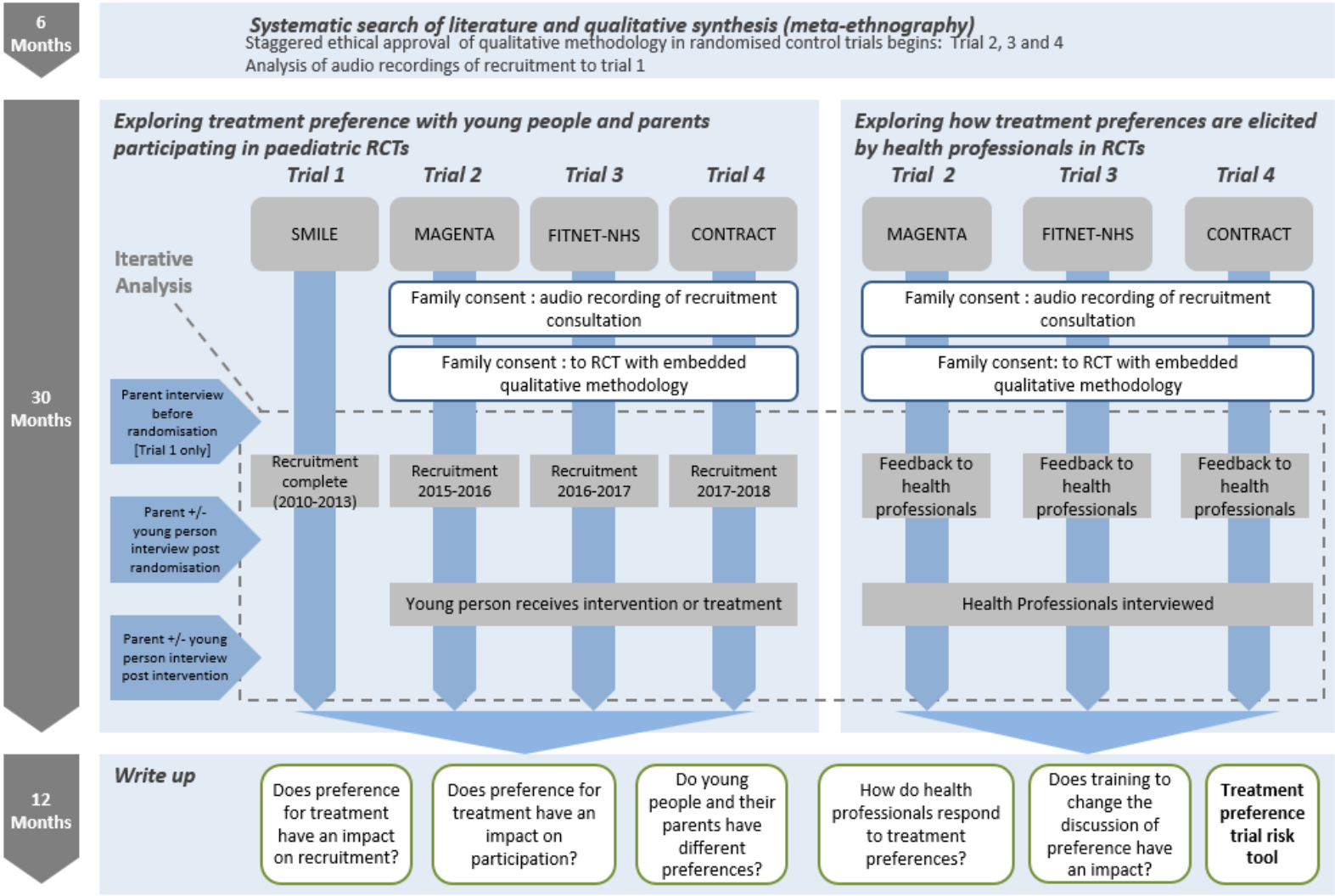


Figure 2:3 Exploring treatment preference with young people, parents and health professionals

2.7 Chapter Summary

This chapter included a detailed overview of the way in which qualitative methods can be used effectively to investigate recruitment processes, specifically preferences for treatment in RCTs. Three paediatric feasibility trials investigating complex behavioural interventions for young people with CFS/ME were introduced (SMILE, MAGENTA, and FITNET-NHS), along with a surgical feasibility RCT recruiting young people with acute uncomplicated appendicitis (CONTRACT). The aim and objectives of this thesis were outlined, along with a figure, (Figure 2:3) providing a visual overview of the way in which preferences for treatment were explored. Qualitative researchers working in any setting are required to think about the concepts of trustworthiness, credibility and transferability when collecting and analysing qualitative data. Key methods of collecting data (such as in-depth interview and audio-recording recruitment consultations), and methods to improve trial conduct (such as communication training for those recruiting to RCTs) were highlighted as useful approaches when exploring recruitment processes in an adult trial context. However, these methods have not been used in a paediatric trial setting; I believe there is scope to do so, therefore Chapter 3 will detail the way in which these methods were used in four paediatric trials that formed the empirical work for my thesis.

Chapter 3: **Methods**

3.1 Overview of Chapter

This chapter details the qualitative research methods drawn upon for data collection and analyses for the doctoral research. This includes an initial rationale for the use of qualitative methods in this research area. Section 3.3 describes the methods used for the systematic search of literature and synthesis of qualitative data. Section 3.4 details the way in which elements of the QuinteT Recruitment Intervention (QRI) were used to inform data collection in each qualitative sub-study, this included: screening, recruitment and retention figures, audio-recorded recruitment consultations and interviews with families and members of clinical teams. Data analyses methods are described in Section 3.5, including methods relevant to each of the four paediatric trials, and the way in which this data were drawn together and analysed collectively. Finally, the ways in which ethical implications were considered are presented in Section 3.6, these included burden and disclosure, researcher reflexivity, safety, lone-working and data related considerations such as anonymity, transcription, storage and transfer.

3.2 Rationale for qualitative methodology

Barbour 2000 highlights the role of qualitative research in relation to its potential contribution to evidence based medicine, defining qualitative research as 'exploratory' and used to address questions of: 'what, why or how', as opposed to questions which seek to quantify evidence or estimate a 'significant difference' between groups. [511] Qualitative research seeks to describe, understand and explain phenomena with an emphasis on context, using methods of data collection (such as interviews or focus groups) which place at the forefront the perspectives of the individuals participating in the research. Barbour also states that '*qualitative research is well placed to provide an enhanced understanding of communication'* [pg. 156] by documenting difficulties or obstacles in the communication process, as well as focusing on language used to convey and provide explanations of events such as diagnosis, treatment and the opportunity to participate in research activities.

O'Cathain recently outlined '*10 rationales*' for using qualitative research methods in RCTs, [401] [pg5-10] one of which is *'to understand complexity'*. Qualitative methods are well placed to explore the complexity of preferences for treatment in paediatric RCTs, since preferences could be expressed by young people, parents or health professionals. Using different qualitative data sources enables exploration of the complexity of recruitment practice, for example, analysis of participant flow, (recruitment figures) in combination with the way in which preferences are communicated, (audio-recorded recruitment consultations) viewed, and experienced (interview with participants).

RCTs operate within the ‘positivistic’ (realist) tradition which assumes there is a ‘truth’ out there to be discovered via the application of rigorous objective and unbiased scientific methods of data collection and analyses. [512, 513] RCTs develop meaning via quantification and establishing a causal relationship between variables under investigation. [464, 514] In contrast, qualitative research methods can be located on a continuum from critical realist (contextualism) [515] to relativism (constructionism). [516] This does not assume that there is a discoverable truth; instead meaning is constructed via discourses which are often based on well-established cultural and political ideologies, e.g. discourses around mental health. [517]

Since I found myself working between the potentially opposing worlds of RCT and qualitative research epistemology (and associated methods), I adopted the ‘middle ground’ of contextualism which does not assume a single reality, but neither does it reject the idea that knowledge can be considered valid in certain contexts. [518, 519] Contextualism also sits with the ‘critical realist’ position which underpins the grounded theory approach was used for data analyses in each of the four RCTs, (see: Section 3.5: Data analyses: Qualitative methods embedded in four paediatric trials). [422] There are multiple possible ‘readings’ or ways of making sense of qualitative data. Researchers play a part in shaping the data collection and analytical processes, (see: Section 3.6.2: Reflexivity). Some methods are linked to an approach or epistemology (such as constant comparison methods and Grounded Theory), while others such as thematic analysis can be applied independently of an epistemological stance.

3.3 Systematic literature review and qualitative synthesis

3.3.1 Protocol and formulating the research questions

I developed and registered the review protocol with PROSPERO: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015942. [520] Scoping exercises were used to define and refine relevant search terms initially the PICOC model was used: Population, Intervention, Comparison, Outcomes and Context. [521]

3.3.2 Eligibility and inclusion criteria

Qualitative or quantitative papers were eligible for review if they reported: i) young people aged 0–17yrs recruited to an RCT: ii) reported either primary RCT outcome(s) and/or secondary findings including embedded/related qualitative studies iii) reported treatment preference for all or some of the participants/parents and iv) any clinical area. Database searches were limited to 1950-2014 inclusive (Appendix 2: Eligibility and inclusion criteria).

3.3.3 Search strategy

A search strategy was developed with guidance from University of Bristol data specialists (NIHR CLAHRC West and Cochrane Group), the search strategy can be found in Appendix 2 (MEDLINE Search strategy). Database searches of MEDLINE, CINAHL, EMBASE, and COCHRANE were carried out. Relevant reference lists and work not published in peer-reviewed journals such as dissertations ('grey literature') were carried out via databases of relevant theses, dissertations and databases

containing registered clinical trials. (http://proquest.umi.com/login, http://www.open.ac.uk/library/library-resources/theses-dissertations, https://www.ukctg.nihr.ac.uk/, https://clinicaltrials.gov/ct2/home http://www.anzctr.org.au/TrialSearch.aspx)

Authors were contacted by email to establish whether full RCT results had been published. Two provided copies of their papers, [325, 522] and three confirmed that they had not yet published findings. [523-526]

3.3.4 Screening and data extraction

Duplicate papers retrieved from database searches were removed using Cochrane Register of Studies (CRS), (desktop version 2015). Each title and abstract was screened for inclusion by two reviewers using the data platform Covidence, (Appendix 2, Title and abstract screening: Inclusion criteria). [527] Discrepancies were documented, discussed and resolved in regular meetings attended by reviewers and the wider systematic review study management team (EC and NM). Questions about the eligibility criteria were addressed in these meetings to ensure that the eligibility criteria were understood and any screening queries were resolved consistently. At the full text review stage papers were read in chronological order by two researchers (LB and AB, HK, RL or RP). Author(s) extracted relevant numeric data and/or descriptive reports of treatment preference into an Excel template (see: Appendix 2: Data extraction fields). These data were summarised (see: Table 4.1) and aggregated (Table 4.2). [528, 529] Qualitative data (participant quotations and first authors discussion points relating to treatment preference) were imported into NVivo for further analysis. [530]

3.3.5 Critical appraisal of synthesised papers

Qualitative papers [66, 74, 96, 97, 107-109, 115, 120, 325, 326, 531] with relevant participant/parent quotations for inclusion in the qualitative synthesis were critically appraised using the Critical Appraisal Skills Programme (CASP) qualitative research check-list (Appendix 2: CASP). [532] Each paper was appraised by two members of the systematic review team (LB and either, AB or RP). Disagreements were discussed by the team members who had appraised the paper and resolved by a senior member of the supervision team (EC). [533, 534] The appraisal tool was used to explore the qualitative papers in more depth, and a sensitivity analysis was carried out to investigate whether leaving lower quality papers out of synthesis altered the qualitative findings. Because this review did not seek to statistically measure treatment preference between trial groups, and due to time restraints and the high number of papers retrieved with relevant descriptive preference data, the remaining 40 papers were not assessed for risk of bias. [8]

3.3.6 Synthesis of qualitative data

Meta-ethnography

The synthesis of qualitative data drew on techniques of meta-ethnography, initially outlined by Noblit and Hare in a seven step process: 1. Getting started, 2. Deciding what is relevant to the initial interest, 3. Reading the studies, 4. Determining how the studies are related, 5. Translating the studies into one another, 6. Synthesising translations and 7. Expressing the synthesis. [535] Qualitative data were extracted from 12 papers (see: section 4.3.2).Qualitative data were imported into the qualitative software package NVivo. [530] Syntheses of data were carried out

primarily by the first author (LB) with supervision, (EC, NM, BY). The scope of the synthesis concentrated on relevant treatment preference data, in the context of the wider aims and findings from the original papers, e.g. the Caldwell paper highlighted a range of parental attitudes to their child's participation in an RCT; only a subset of themes/concepts in the original paper indirectly related to expressions of preferences for a treatment group.

Data were structured using Schutz's concepts of first (participant quotations) and second (authors' analyses) order constructs. [536] Authors' original themes and interpretations were organised in NVivo 'node' and 'mapping' structures, with relevant quotations (Appendix 2, Example: meta-ethnography – second order constructs). Concepts from individual papers were translated into one another (a reciprocal translation) to develop evolved interpretations (see: Meta-ethnography: Translation of first, second, and third order constructs). Third order constructs were taken forward as a line of argument in a new interpretive context: expressions of treatment preference. [537-539] Synthesised data were reviewed by the wider supervision team (EC, NM & BY) one of whom was an author on two of the original papers included in the synthesis (BY) and colleagues (AB and RP).

3.4 Data collection: Qualitative methods embedded in four paediatric trials

The qualitative work presented in this thesis was carried out in collaboration with four paediatric RCTs, three focusing on treatment for CFS/ME, and one surgical trial focusing on treatment for appendicitis (see: Section 2.4). Each trial received ethical approval from relevant research ethics committees, (Appendix 1: Ethical approvals) and all were registered on the ISRCTN registry. An overview of each collaborating RCT can be found in Table 2.2.

3.4.1 Recruitment and retention figures

Recruitment and retention figures were evaluated as each trial progressed; figures relating to number of eligible patients assessed, recruited, declined, withdrawn and discontinued treatment were reviewed on a month-by-month basis. These figures were reported at relevant TMG and TSC meetings and were used to inform purposive sampling (see: Section 3.4.6) for family and health professional interviews in each of the four trials.

3.4.2 Audio-recorded recruitment consultations

Recruitment consultations were audio-recorded with written assent/consent for the recording from parents and young people in all four trials. This is a novel method used initially by colleagues working on the ProtecT study and is now used routinely as an ongoing part of the QRI approach. [408, 540] Those recruiting to each collaborating RCT were asked to routinely record every recruitment consultation they

had with all eligible families who were given information about each RCT. Recordings were deleted if families decided they did not want the recording to be used for research purposes. See Appendices 3, 4, 5, and 6 for further details of data collection and randomisation in each trial setting.

During the SMILE and MAGENTA trials recruitment consultations were conducted within one month of the young person's first clinical appointment with the specialist CFS/ME service. In the SMILE RCT consultations were conducted face-to-face with the recruiter in the family home. In the MAGENTA RCT most consultations were conducted via telephone, some were conducted at the local hospital if the family preferred. If families declined participation in the MAGENTA trial the recruiter recorded whether this occurred before or after verbal discussion of the trial had taken place, and reasons for decline were discussed when these were offered by young people and parents. In the FITNET-NHS RCT all consultations were conducted via telephone and were preceded by an eligibility assessment since young people lived out of area and had not had a face-to-face consultation with the specialist service diagnosing CFS/ME. Recordings of the eligibility assessment with families could not be made during the FITNET-NHS trial, because research consent had not yet been obtained from families, therefore recordings were only made when families declined the trial at the recruitment consultation stage. See Appendices 3, 4, 5 and 6 for further details of the eligibility assessment in each trial setting.

3.4.3 Interviews with young people and their parents

Each trial PIL (Appendices 3, 4, 5, and 6) stated that a subset of families would be contacted by a researcher to discuss the trial in greater detail. This was described as an optional interview(s) that families could participate in, in addition to participation in the main trial. Young people were eligible to take part in an interview as part of each embedded qualitative study dependent on the following age criteria: SMILE: 12-18yrs, MAGENTA: 8-17yrs, FITNET-NHS: 11-17yrs and CONTRACT: 7-15yrs). Parents of all young people eligible for each trial could participate in an interview.

Families who declined RCT participation in the SMILE, MAGENTA and CONTRACT trial were invited to take part in an interview. Consent for interview (contact from the research team) was not obtained from families who declined the FITNET-NHS trial, therefore only those who consented to the trial were able to participate in a qualitative interview. Table 5:5 provides a breakdown of the number of families who participated in interviews.

During the SMILE RCT (prior to this PhD) I interviewed parents at three time points: 1. After initial assessment and before randomisation, 2. After randomisation and before the intervention, and 3. After the intervention. This provided a clearer understanding of how families experienced the prospect of RCT participation prior to randomisation and how they experienced the process of randomisation and their later involvement in the RCT interventions.

During the MAGENTA, FITNET-NHS and CONTRACT trials families participated in one interview at various time points post randomisation. During the MAGENTA trial this was either after randomisation or after having received 6-months of their allocated intervention. FITNET-NHS families were interviewed at the early, mid or late stage of their allocated intervention so that the acceptability of the interventions could be explored. CONTRACT families were interviewed 1-4 weeks after discharge from hospital where possible. The Contribution Statement provides details of all those involved in data collection for each individual trial.

Interviews with young people participating in the CONTRACT trial were up to 30 minutes in duration. Parent interviews were up to an hour long, and Interviews were audio-recorded with written consent, transcribed verbatim, and anonymised. Interviews followed a checklist of topics to ensure consistency, (see: Section 3.4.5: Interview topic guides).

3.4.4 Interviews with clinical teams

Recruiters and members of each clinical team were invited to be interviewed, to gain insight into their perceptions of trial processes and progress. Health professionals were purposively sampled (see: Section 3.4.6), to take part in an interview if they recruited participants or delivered RCT interventions in three of the collaborating RCTs (MAGENTA, FITNET-NHS and CONTRACT). Most health professionals were interviewed only once, but there was scope to interview at more than one time point. Health professionals were interviewed on more than one occasion if specific areas of

interest arose during recruitment consultations, or when health professional practice changed. Table 5.8 provides details of the number of health professionals who participated in interviews.

3.4.5 Interview topic guides

Semi-structured interviews were conducted in each of the nested qualitative studies reported in this thesis. Each topic guide followed a checklist of topics to ensure consistency and can be found in Appendices 3, 4, 5, and 6. Each topic guide covered questions relating to prior knowledge of the interventions, beliefs, expectations and preferences about both interventions, the recruitment process, acceptability of written and verbal information provided, and experiences of the interventions. During interviews, parents and young people were encouraged to raise issues they felt to be relevant and important. Initially the topic guide was developed by NM for the SMILE RCT (Appendix 3). I developed and updated the topic guide for use in the MAGENTA trial, comments were provided by NM in relation to changes to questions, specifically making questions about preference less direct (Appendix 4) The MAGENTA topic guide was used as a template for FITNET-NHS and CONTRACT trials, with additional comments from NM and BY prior to participant recruitment, and in collaboration with RP and FS as recruitment progressed (Appendices 5 and 6)

3.4.6 Sampling and sample size for interviews

Sampling was initially guided by each trial protocol and included a range of participant characteristics in terms of age, sex, and where possible socioeconomic circumstance, as well as participants from both intervention groups (maximum variation sampling). As recruitment progressed, and by drawing on recruitment consultation data I was able to target participants with characteristics of interest (e.g. preferences for treatment or discontinued treatment) to follow-up and develop findings. I purposively sampled families to take part in qualitative interviews during the SMILE and MAGENTA RCTs. [541] Purposive sampling specifically targeted families who declined to participate, those who expressed a preference for treatment during recruitment consultations but went on to participate in the RCT and those who discontinued treatments. [542]

I also actively approached fathers for their views in relation to their child's participation, because no fathers were available to provide feedback during the SMILE RCT. I worked collaboratively with other qualitative researchers responsible for conducting interviews during the FITNET-NHS and CONTRACT trials (RP and FS) to ensure that families were not only purposively sampled to include a range of 'participant' characteristics, (such as age, sex and trial group) but also those who discussed preferences for treatment during recruitment consultations. All consultation recordings were listened to as they became available from each clinical team.

Due to the nature of CFS/ME (the potential for fluctuation in symptoms), some participants who were purposively sampled for interview postponed or declined the interview request. Some parents declined the opportunity for their child to take part in an interview during the CONTRACT trial, or young people themselves declined because they had a poor recollection of the recruitment process due to pain from their appendicitis (Table 5:5: Families approached and interviewed).

Health professionals were purposively sampled to take part in an interview when they had either discussed the trial with two or more prospective families (those recruiting participants during CONTRACT) or had been delivering trial interventions for approximately five months (MAGENTA and FITNET-NHS). Recruiters who had discussed the trial with families who had declined were initially contacted for interview. Where possible, members of the wider clinical team who were not involved in recording recruitment consultations (e.g. ward nurses and senior surgeons), were also contacted to gain information in relation to wider team equipoise. Health professionals working with young people who had discontinued CFS/ME treatment during the MAGENTA trial were also approached for interview. Due to high workloads and difficulties scheduling interviews with busy clinical teams, the majority of those who provided recruitment consultations (CONTRACT) and all members of the CFS/ME specialist service team were contacted to take part in an interview (Table 5.8 Health Professional Interviews).

The interview sample sizes in each trial were determined by data saturation, i.e. when data analyses showed no new themes in the data. [543] I estimated that between 20-

30 interviews with families, and 10-25 interviews with health professionals would be conducted in each trial. However, more health professional interviews were carried out than initially anticipated, to gain additional feedback into recruiter and wider team equipoise (see: Section 5.3.4: Health professional and recruiter equipoise). Family interviews could include separate interviews with a young person and then their parent, (individually), or a joint interview where a young person and their parent(s) were interviewed together if preferred by the family.

3.4.7 Patient and Public Involvement (PPI)

Patient and public (PPI) involvement and feedback were sought during the development phases of each of the four RCTs in which qualitative methods were embedded. Patient information sheets, consent forms and each interview topic guide were reviewed by PPI members before and during each of the four RCTs. Detailed information relating to the way that PPI was developed and informed trial documentation can be found in Appendix 12.

3.4.8 Training: communicating equipoise in paediatric trials

Training for recruiters in the four paediatric trials developed and changed in structure from basic one-to-one feedback discussions in 2010, (SMILE RCT) to structured group feedback sessions in 2015-2017 (MAGENTA, FITNET-NHS and CONTRACT RCTs). Early training in the SMILE RCT was developed with specific reference to work carried out by Professor Jenny Donovan and colleagues in the ProtecT study. [98, 123, 207] Training in later trials (MAGENTA, FITNET-NHS and CONTRACT)

also drew on findings from the Quintet Recruitment Intervention (QRI) (see: Section 2.2: Qualitative research and adult randomised controlled trials). [127, 177, 246, 408, 540] Those recruiting to each collaborating RCT were asked to routinely record every recruitment consultation, (section 3.4.2) and these recordings formed the basis of ongoing training as each trial progressed, see Appendices 3, 4, 5 and 6.

3.5 Data analyses: Qualitative methods embedded in four paediatric trials

Thematic analysis techniques which drew on constant comparison and grounded theory were used during the course of each trial. Subsequently themes and findings from each of the four trials were compared, contrasted and integrated using framework analysis. [544] Each analysis method is discussed in turn in the following sections.

3.5.1 Thematic analysis

Data from four trials were included in this thesis, SMILE data which I had already collected and analysed (Secondary analysis: SMILE RCT 2010-2013), and data collected during three prospective trials (MAGENTA, FITNET-NHS and CONTRACT). Methods of constant comparison derived from grounded theory were used to analyse recruitment consultation and interview data in each of the four trials as each trial progressed. [545-547] Analysis was an iterative process and informed further sampling in each individual trial. Constant comparison methods were used to

identify common or divergent themes using thematic analysis. [458, 548] Recruitment consultation and interview transcripts were coded using NVivo. [530] I regularly fed back qualitative findings from each trial to relevant TMG and qualitative sub-study meetings so that findings were reviewed by the wider team members, and changes to study processes could be made as each trial progressed.

Secondary analysis: SMILE RCT 2010-2013

Prior to starting this PhD, I conducted the qualitative interviews for the SMILE RCT, these data were included in this thesis. I conducted interviews with parents at three time points (before recruitment consultations, post randomisation and post intervention). Young people were only interviewed at one time point to avoid burden, either post randomisation or post intervention. Family interviews and recruitment consultation data were collected and analysed drawing on techniques of constant comparison, grounded theory and thematic analysis.

PhD data analysis

SMILE: Secondary analysis

I retrospectively listened to all SMILE recruitment consultations. All relevant preference related data were extracted from earlier NVivo coding structures (recruitment consultations and family interviews). I re-familiarised myself with earlier thematic analysis carried out with SMILE data, by reviewing coding structures. I re-read recruitment consultation and interview transcripts, reflexive notes, analytic memos and descriptive accounts. I transcribed relevant sections from all

consultations that had not already been transcribed and analysed (those conducted towards the end of the trial in 2013). [547]

MAGENTA, FITNET-NHS, CONTRACT: Prospective data collection and analysis

During the MAGENTA, FITNET-NHS and CONTRACT trials analyses was carried out as each trial progressed. Separate NVivo projects were created for each trial, and separate coding structures were created for each data type (recruitment consultation, family and health professional interviews). I initially listened to each recruitment consultation and took notes, each consultation was then transcribed (see: Section 3.6.4: Anonymisation, transcription). Interview and recruitment consultation transcripts were imported into NVivo and coded using an inductive open coding approach. [549] Data-derived codes (from recruiters' and participants' own words, or in-vivo coding) were created. As more transcripts were coded categories and concepts were developed via an iterative process of constantly going back and forth between data sources (recruitment consultations and interviews), analytic memos and discussions with colleagues (EC, NM, BY, FS, RP). [458] Descriptive accounts and reports of findings were developed and revised as each trial progressed. I cross-referenced data from recruitment consultations with matching interview data where possible. This cycle continued iteratively as more data were collected and analysed during the course of recruitment to each trial. I kept reflexive notes recording contextual information; this included information about the young person's condition, (mild or moderately affected) family circumstances and parents' and young persons' preferences for treatment interventions.

I paid particular attention to: possible justifications for expressions of preference, misunderstandings related to communication in recruitment consultations, language used by those recruiting that may have influenced families' preferences for trial interventions and the way in which recruiters responded to families' preferences for trial interventions. I also focused on the way in which recruiters accepted or explored treatment preferences expressed by young people or their parents (recruitment consultation data), and the justifications provided by young people and parents for declining or participation (interview data). Families who expressed views that were unexpected or whose recruitment practices were 'different' were studied in detail as 'negative cases'. [550] This included instances where treatment preferences differed between parent and child, and families who expressed preference for treatment but consented to the trial.

Care was taken to distinguish between themes and findings that were specific only to young people, parents or health professionals. Ten percent of the qualitative data were independently coded by another team member (DJ, NM, RP, FS) to enhance coding reliability. [359, 360] These data were discussed collectively by each qualitative sub-study group, which included senior members of each research team (EC, NM & BY). Discrepancies were resolved via modification of coding categories where necessary. To compare and contrast common and divergent findings across the four trials, the final analytic stage involved combining data from multiple trials and sources. Framework analysis was used to compare codes and themes across data sets (see: Table 5:9 Thematic framework) encompassing similar (and contrasting) themes and findings from each RCT. Throughout the analyses I also considered the

context of each individual trial, [458] and the way in which previous data analyses affected later data collection and analyses.

3.5.2 Content analysis

Content analytic methods are not always associated with qualitative approaches to data analyses since they generally involve the ‘counting’ of words or content. [551] However, qualitative content analysis also seeks to understand the context in which words and conversation are used, [552] and involves a basic ‘interpretation’ of the data under analysis. [553] A deductive and directed content analysis was used to retrospectively analyse recruitment consultation data from the SMILE RCT. [554-556] The approach was deductive because it used coding categories that were predefined and derived from analysis of data from a previous adult RCT. [123, 405] This analysis aimed to understand how and when young people and their parents expressed preference for treatment.

An existing checklist which categorised preference as: definite, probable, or not stated was used (developed by NM, Appendix 3: Content analysis checklist). This content analysis was directed because it was based on prior knowledge of the research area under investigation, given that a thematic analysis of SMILE trial consultation and interview data had already taken place. The checklist was used to record whether treatment preferences were expressed by young people and their parents. The number of young people and/or parent(s) who expressed the following were counted: 1. A preference or non-preference (dislike) for treatment ‘at outset’ before randomisation. 2. If provided the key reason(s) for preference were recorded,

and whether or not the preference was ‘definite’ (repeated at various points in the discussion) or ‘probable’ (the individual expressing the preference seemed unsure, changed their mind or didn't give reasons for their preference). 3. As the consultation progressed, a judgement was made in relation to whether the preference or non-preference appeared to be entrenched or dispensed with at the end of the consultation. The outcome of the recruitment consultation, e.g., randomised or declined participation was also recorded. Instances where the young person and/or parent expressed a preference or non-preference after the young person had agreed to randomisation and had been given their intervention allocation were recorded. The category ‘can't tell / preference not stated’ was used if the young person or parent(s) verbal response to questions relating to preference were not expressed or explored by the recruiter during recruitment consultations.

The aim of this analysis was to understand the frequency and perceived ‘strength’ of expressed preference (definite or probable) for treatment in paediatric recruitment consultations. This also provided important contextual information in relation to whether it was the patient or parent (or both) expressing preference, and the timing of expressions of preference, whether they were made before or after randomisation and treatment allocation. These findings are explored in detail in Chapter 5, Section 5.3.1: How and when preferences are expressed.

3.6 Ethical Considerations

3.6.1 Burden and disclosure

An ethical issue relating to this research was the potential for additional burden on young people and their wider family. Interviews with young people who were currently unwell (with CFS/ME), or those who were being asked to recall a stressful acute episode of ill health (appendicitis) could be a burden, distressing or upsetting. I ensured that all interviews with young people diagnosed with CFSME were no longer than 20-30 minutes, with rests during the interview if appropriate. Interviews with young people participating in the CONTRACT trial were also monitored so that they were appropriate for the age of the young person taking part.

I worked closely with recruiting health professionals, study primary investigators and health professionals delivering clinical care so that all relevant information about participants' health conditions (e.g. recent increase in CFS/ME symptoms or a particularly unpleasant infection after appendicitis surgery) were taken into consideration when arranging interviews. Young people were given the option of interview with, or without their parent(s) being present. I ensured that young people were well enough to take part in interviews by checking with them (or their parents if they were 15 years old or under) the day before or the morning of the interview, to ensure that any vulnerable young people, (e.g., those experiencing more moderate symptoms of CFS/ME) were not overburdened. Interviews were cancelled if the young person was unwell, and rescheduled where possible.

Another potential issue was that of disclosure during the qualitative interview. At the beginning of each interview all participants (young people, parents and health

professionals), were informed of their right to confidentiality, and it was stressed that information discussed during interviews would not be passed on to the health professionals delivering clinical care, or in the case of health professionals, other members of the clinical team. I also highlighted that information would only be shared with a third party in instances where I believed that a participant was at risk of harm. I also informed participants if elements of the interview were to be disclosed because of concerns about welfare, this would always be discussed with them at the end of the interview.

3.6.2 Reflexivity

A qualitative researcher is an ‘active’ part of the research process. [557] A researcher’s age, sex, perceived social class and professional role are all likely to have an impact upon interaction during data collection, influencing the way in which participants disclose information and the way in which researchers ask questions. I told families that I was not a ‘medically trained’ person, neither was I a member of the clinical team they had seen ‘at the hospital’. [558] However, my status as someone who worked ‘for a university’ was disclosed, [559] and was likely to have affected the way in which families perceived me. I always highlighted that participants were the ‘experts’ and I was interested in what they had to say, both positive and negative. I made an effort to develop a ‘friendly but professional’ rapport with parents and young people, and reflected on occasions when young people or parents may have wanted me to overstep these professional boundaries. [560]

I also reflected on the way in which my professional role as a researcher might influence data collection and my approach to the analyses of that data. [561] I had

some knowledge of the research area when I started this PhD, therefore my 'pre-conceptions' about the research area may have influenced the probing questions I asked during interviews. I may have focused upon preference more than my colleagues without an interest in this research area. I kept reflective notes as each trial progressed and strove to remain open minded during data collection and analyses, and frequently discussed findings with members of the wider trial teams. [562, 563] I also reflected on the way in which my clinical colleagues (particularly those working on the wider CFS/ME specialist team) may have felt about discussing their views and opinions with me during interviews, as someone they knew and had worked with for a number of years. [454, 455]

3.6.3 Researcher safety and lone working

It is necessary to ensure that suitable systems are in place for contacting research staff when they are working alone and away from their usual place of work. FITNET-NHS protocol stated that all interviews would be conducted via skype or telephone. During SMILE, MAGENTA and CONTRACT trials researcher protocols stated that participants would be given the option of being interviewed in their own home. The risks of lone working can include increased vulnerability to verbal and physical aggression and isolation from timely help and support in situations of equipment failure, accident and illness.

Researcher safety was considered carefully in each paediatric trial prior to, during, and following participant interviews, some of which were scheduled outside of normal working hours. Travel to interviews required that I drive long distances, sometimes to towns and cities that were not known well to me or the research teams

during hours of darkness at certain times of the year. Local NHS lone working procedures from each sponsor/trust were reviewed by researchers working on each of the three RCT. However, unlike NHS staff who undertake external home visits, research staff did not have access to records where issues of potential risk within households or neighbourhoods might be documented. I developed procedures for SMILE, MAGENTA and CONTRACT lone working, (Appendix 10) with reference to University of Bristol School of Social and Community Medicine Fieldwork Safety Policy.

3.6.4 Anonymisation, transcription

Anonymisation requires the removal of name, address, full post code and any other detail or combination of details that might support identification. Anonymised information does not identify an individual directly, and cannot reasonably be used to determine identity. [564] A participant 'qualitative' identifier code (e.g. Young person 20) was linked to each participant's trial research code and used as a 'pseudonym' for all families who consented to a recording of their recruitment consultation, or who participated in interviews. All participant identifiers were pre-fixed with a letter corresponding to the trial (e.g. 'C' – CONTRACT Young person C20). Upon transcription, all identifiable information was removed so that it was not be possible to identify any individuals. A sub-set of recruitment consultations from the SMILE RCT were transcribed professionally, and I transcribed relevant sections of all remaining recruitment consultations retrospectively. I also transcribed relevant sections of recruitment consultations as soon as they became available during the MAGENTA trial. All remaining recruitment consultations and interviews (FITNET-

NHS and CONTRACT) were securely transferred to two external, approved transcription companies who held confidentiality agreements with either the University of Bristol or University of Liverpool. Both companies transferred all files via secure sockets layer (SSL) or transport layer security (TLS) protocols, with advanced encryption standard (AES) 256-bit while in transit and at rest on their server.

3.6.5 Storage and transfer of data

All qualitative data were stored securely during the course of each RCT in accordance with University of Bristol and local NHS Data Protection Policies. [565] This included precautions to avoid physical loss or damage of electronically stored data. Access to electronic records containing identifiable participant information was restricted to members of the relevant research teams via University of Bristol servers, with access assigned and maintained by University of Bristol IT services. All electronic records containing identifiable participant information were also password protected, this included electronic copies of signed consent and assent forms. All paper records (with details pertaining to families and health professionals who participated in the trials) were kept in locked cabinets within areas of the Universities of Bristol and Liverpool with restricted university secure card access. All other data (such as recruitment consultation and interview transcripts), were stored securely in another secure, locked cabinet.

Care was taken when paper or electronic records were taken away from the University of Bristol (e.g. en route to family interviews). Digital recorders used to store and transfer interview discussions from families' homes or NHS sites to

university sites (and to transfer recruitment consultation data during the SMILE trial) were encrypted to ensure secure transportation. I developed procedures for transferring audios from the encrypted digital recorders to secure university servers (Appendix 11) and all files were then deleted from devices.

Recruitment consultation data were transferred electronically via secure data transfer systems, (Research Data Storage Facility and DatAnywhere) approved by either the University of Bristol or University of Liverpool during the MAGENTA, FITNET-NHS & CONTRACT trials. Nominated members of each clinical team at each trial site were responsible for uploading all recruitment consultations from digital recorders to transfer systems. It was not necessary for audio files to be re-accessed by any NHS personnel at collaborating NHS sites after the initial data transfer process, so all data were stored securely on University servers and deleted from devices held in NHS sites.

Consent and assent were managed via the Research Electronic Data Capture (REDCap) system during the MAGENTA and FITNET-NHS trials since the majority of recruitment consultations were conducted by telephone. [566] I developed two REDCap projects with support from the University of Bristol REDCap technical support team (prior to this PhD). Projects were stored on secure University of Bristol servers, and an electronic consent URL (secure webpage) was sent by the recruiter to an email address specified by parents or directly to young people aged 16-17 years. Young people and parents were able to use this URL to access age appropriate electronic web-based assent and consent forms. These forms could be

accessed and submitted either in real time, or at an agreed point in the future if families wanted more time to consider trial participation. Interviews completed via skype or telephone also used the same REDCap system to gain consent and assent from participants and health professionals.

3.7 Chapter Summary

This chapter detailed the research methods used during this PhD thesis in two key areas: 1. The systematic review of paediatric preference literature and synthesis (meta-ethnography) of qualitative data retrieved via the systematic review. 2. The collection and analyses of data from four paediatric RCTs. Elements of the QuinteT Recruitment Intervention (QRI) approach were used to inform data collection and analyses methods during the latter. [408] Data from all four trials were drawn together and analysed collectively using framework analysis. Finally, relevant ethical considerations: burden, disclosure, researcher safety and lone-working were discussed, along with data management considerations (anonymity, transcription, storage and transfer). The next two chapters describe findings from the systematic review and qualitative synthesis (Chapter 4) and findings from the four paediatric trials with embedded qualitative methods (Chapter 5).

Chapter 4: Findings – Systematic literature review and qualitative synthesis

4.1 Overview of chapter

This chapter reports the results and discussion points raised from the systematic review of literature relating to treatment preference in paediatric RCTs, and the synthesis of qualitative data. Section 4.2 details analysis of 'descriptive' preference related data extracted from 40 papers, and Section 4.3 synthesis of 'qualitative' data (relevant quotations and first authors' analyses) extracted from 12 papers. This chapter also includes a discussion (Section 4.4) of the strengths, limitations and links to previous literature. The implications for future practice and implications for future systematic reviews in this area are also considered.

4.2 Summary of included studies (descriptive data)

Database searches retrieved 23,449 papers, and additional searches yielded 101 papers. After deduplication, title and abstract screening was carried out on 17,036 papers, and 676 were read in full, with 52 papers eventually included in analyses (see: Figure 4:1). Table 4:1 describes all the papers included in the systematic review, 27 reported data from RCTs conducted in the UK and Europe and 23 elsewhere, (USA, Canada, Australia and Brazil). Most papers were published from the year 2000 onwards (n = 42). Searches were carried out to locate primary trial papers for secondary papers included in the review and 18 were located. [115, 567-

583] It was not possible to find all the primary trial papers because some secondary papers did not explicitly use identifiable trial names or registration numbers.

Of the 52 papers, seven reported findings from multiple trials, [96, 97, 107, 325, 326, 584, 585] and two were abstracts from poster presentations. [523, 524] Forty-two of the papers reported 'conventional' RCTs, [74, 94, 96, 97, 107-109, 120, 220, 319, 323, 325, 326, 381, 522-526, 531, 585-606] two of which were in the feasibility or pilot stages. [586, 587] Eight papers described RCTs with parallel 'preference' groups at trial outset, [66, 607-613] and two introduced preference groups due to slow recruitment. [584, 614] Seven papers reported trials using participant blinding or double blinded, [319, 381, 526, 594, 599, 605, 606] and all remaining papers reported unblinded non-inferiority/equivalence RCTs. Ten papers reported use of a placebo arm [96, 97, 107, 319, 326, 381, 526, 594, 605, 606]

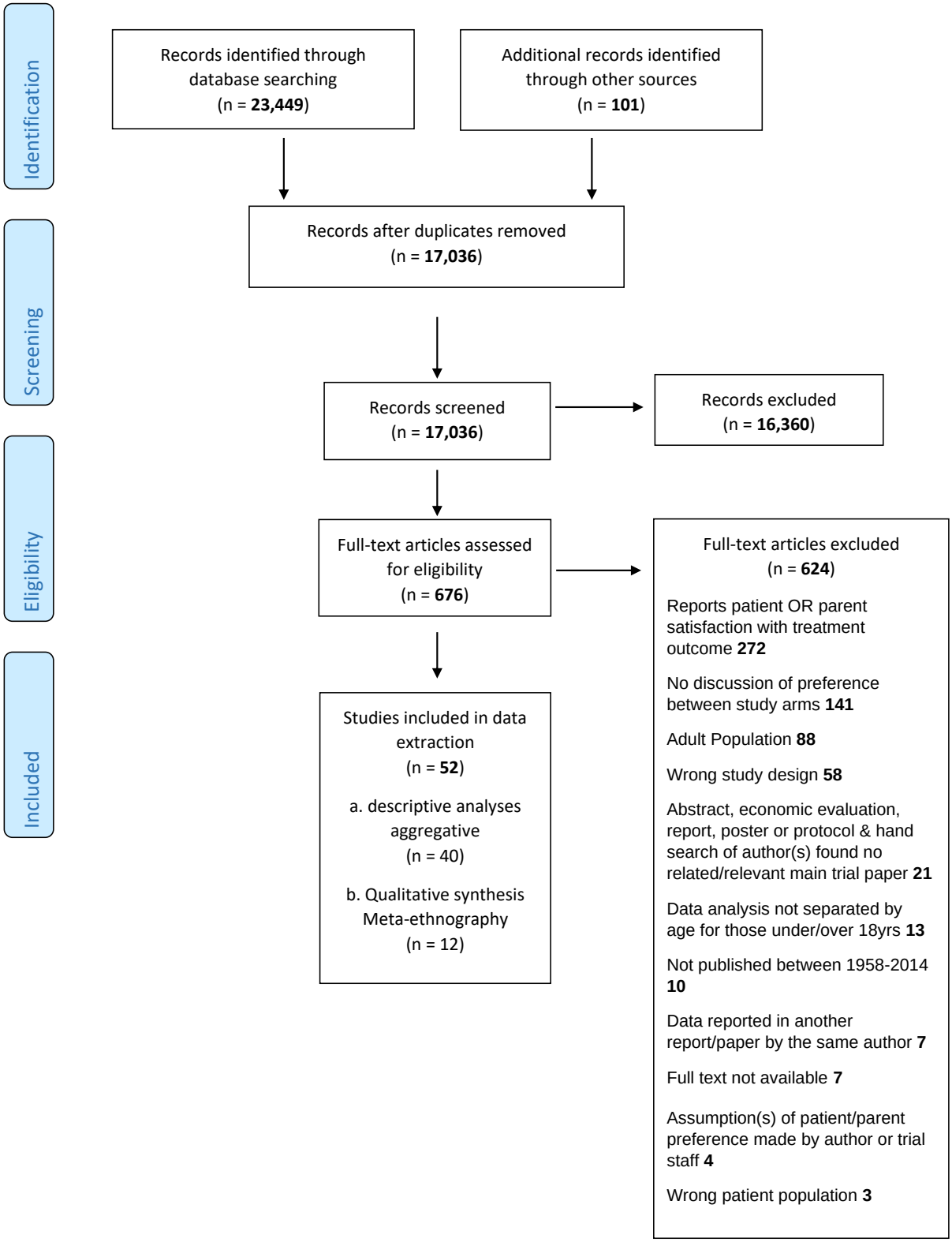


Figure 4:1 PRISMA flow diagram of included studies

[615]

Table 4:1 Systematic review of literature: Included papers

Conventional RCTs (n=42)			
Author	**Paper type (primary or secondary paper*)**	**Participant age**	**Trial aim**
Allen 2013 [586]	Primary (Feasibility)	13-17yrs	Assessed feasibility of recruiting young women into an RCT of caseload midwifery.
Allmark 2006 [531]	Secondary Primary paper Azzopardi 2009 [569]	≥36wks	Compared intensive care plus total-body cooling for 72 hours with intensive care without cooling among term infants with asphyxial encephalopathy.
Banks 2012 [587]	Primary (Pilot)	5-16yrs	Assessed feasibility of carrying out a fully powered RCT comparing care of childhood obesity intervention (COCO) and a primary care clinic intervention (PCC).
Barratt 2013 [220]	Secondary Primary paper Wake 2009 [581]	5-10yrs	In-depth understanding of why families chose not to participate in a community-based study on childhood obesity.
Bauchner 1996 [588]	Primary	3mth-6yrs	Do parents prefer antibiotic administration for treatment of acute otitis media by a single intramuscular (IM) injection or standard oral therapy for 10 days.

Blickman 2013 [589]	Primary	1-12yrs	Assessed the impact of a Certified Child Life Specialist (CCLS) on parent satisfaction, staff satisfaction, child satisfaction, and parent and staff perceptions of child pain and distress in a paediatric imaging department.
Byrne-Davis 2010 [109]	Secondary Primary paper Vora 2013 [580]	2-11yrs	Examined how recruitment looked to an observer and how it felt to parents, (of children with low-risk acute lymphoblastic leukaemia) to identify how doctors' communication could promote or inhibit optimal recruitment.
Caldwell 2003 [97]	Secondary (Multiple RCTs)	Not stated	Explored parents' attitudes to children's participation in trials, identifying factors that influenced decision-making and perceived risks and benefits. RCTs included oncology and renal: interventions not defined.
Carvalho 2013 [120]	Secondary Primary paper Moreira 2013 [577]	<3yrs	The understanding and perceptions of mothers regarding the informed consent and randomisation processes linked to an RCT that compared behaviour management techniques for paediatric dental sedation.
Chappuy 2014 [522]	Secondary	Children - age not stated	Parental and child understanding of RCT participation (Acute lymphoblastic leukaemia FRALLE 2000A protocol) and evaluations of the readability of written documents provided.
Duncan 2004 [590]	Primary	11mths-12yrs	Effectiveness of osteopathic manipulation, acupuncture or wait list control as a 6-month therapeutic adjunct for children with spastic cerebral palsy.

Eiser 2005 [108]	Secondary Primary paper Mitchell 2005 [576]	4-16yrs	Mothers' (of children newly diagnosed with Acute Lymphoblastic Leukaemia: ALL) views regarding consent to randomised controlled trials.
Forsander 1995 [591]	Primary	12-15yrs	Evaluation of family attitudes in relation to the two 3wk care systems for diabetes management: early discharge from ward to training apartment and treatment on a ward in paediatric clinic.
Glogowska 2001 [323]	Secondary Primary paper Glogowska 2000 [115]	3-4yrs	Reported attitudes of parents whose child took part in a speech and language therapy RCT comparing immediate treatment and watchful waiting.
Harth 1990 [319]	Secondary Primary paper Van Asperen 1992 [578]	6mths-3yrs	Double-blind, placebo-controlled trial of ketotifen, a new and unlicensed (for Australia) oral asthma drug.
Hissink Muller 2011 [523]	Secondary (poster presentation) Primary paper Hissink Muller 2017 [574]	Children - age not stated	Comparison of three treatment strategies, and feedback relating to treatment preferences among parents of patients with recent onset juvenile idiopathic arthritis.
Hissink Muller 2012 [524]	Secondary (poster presentation) Primary paper Hissink Muller 2017 [574]	12-18yrs	Comparison of three treatment strategies, and feedback relating to equipoise among parents and patients with recent onset juvenile idiopathic arthritis.
Johnson 2007 [525]	Secondary	10-18yrs (and adults)	Assessed participant and parent experiences in the parenteral insulin group of the Diabetes Prevention Trial (DPT-Type 1).

Johnson 2009 [526]	Secondary	10-18yrs (and adults)	Assessed the experiences of participants and parents of children in the oral insulin study of the Diabetes Prevention Trial (DPT-Type 1).
Jollye 2009 [326]	Secondary (Multiple RCTs)	Neonates	Explored the thoughts and feelings of parents in their decision-making process, in either choosing or declining to participate in neonatal RCTs.
Levi 2000 [585]	Secondary (Multiple RCTs)	2-18yrs	Retrospective parent perceptions of communication of their child's cancer diagnosis and the informed consent process.
Miner 2007 [592]	Primary	6mth-17yrs	To determine if nebulised fentanyl is a feasible alternative to IV fentanyl for the treatment of acute pain in children presenting to the emergency department (ED) with painful conditions.
Payne 2004 [593]	Secondary	3-12yrs	Views and preferences for anaesthetic related issues important to parents (and adults) who took part in a prospective RCT.
(PENTA) Paediatric European Network for Treatment of AIDS 1999 [594]	Secondary (double-blind)	Children - age not stated	Described parents' experience of their child being enrolled in a HIV infection RCT, including the degree to which it interfered with life, and their feelings about use of deferred (placebo) and immediate antiretroviral treatment.

Rovers 2000 [595]	Primary	16-24mths	The effectiveness of ventilation tubes on the language development in infants with persistent otitis media with effusion (OME) compared to watchful waiting (WW).
Sammons 2007 [94]	Secondary Primary paper Atkinson 2007 [568]	6mth-16yrs	Parental views on the informed consent process, information provided, reasons for taking part and willingness to participate in future research. Compared motives of British and European parents.
Sandler 2014 [596]	Primary	12-18yrs	Effectiveness of 3 methods of orthodontic anchorage supplementation, reporting orthodontists' and patients' values.
Sartain 2002 [597]	Primary	6wks-12yrs	Assessed the clinical effectiveness of a paediatric hospital at home service compared to conventional hospital care.
Schuttelaar 2010 [598]	Primary	≤16yrs	Compared the level of care from nurse practitioners with care delivered by dermatologists.
Sederberg-Olsen 1998 [599]	Secondary (double blind) Primary paper Balle 1998 [570]	1-10yrs	Evaluated the efficacy of amoxicillin-clavulanate and penicillin-V in the treatment of secretory otitis media (SOM).
Shilling 2011 [96]	Secondary (Multiple RCTs) MASCOT: funding extension application rejected & trial closed prematurely [575]	MASCOT: 6-15yrs	Identify strategies to improve recruitment and trial conduct, by comparing practitioners' and parents'

	MENDS [567] POPs [still recruiting] TIPIT [583]	MENDS: 3-15yrs POP: 4-18yrs TIPIT: < 28wks	accounts of the invitation to enter a child into clinical trials.
Snowdon 1997 [74]	Secondary Primary paper UK Collaborative ECMO Trial Group [573]	Neonates	Exploration of parental reactions to random allocation of treatment in a neonatal RCT comparing two methods of life support, conventional management (CM) and extracorporeal membrane oxygenation (ECMO). Recruitment was stopped early, because data showed a clear advantage with ECMO.
Spandorfer 2005 [600]	Primary Loss of clinical equipoise and declining accrual rates led to trial termination.	8wk-3yrs	Compare oral rehydration therapy (ORT) and intravenous fluid therapy (IVF) in the treatment of viral gastroenteritis.
Sureshkumar 2012 [381]	Secondary Primary paper Craig 2009 [571]	<18yrs	To identify modifiable and unmodifiable factors associated with parental consent to a trial investigating long-term, low-dose antibiotics in preventing recurrent urinary tract infection.
Tercyak 1998 [601]	Secondary Primary paper Diabetes Control Complications Trial Research Group [572]	11-18yrs	Identify reasons/characteristics of adolescents who refuse or consent to participate in an RCT of intensive therapy (IT) for insulin-dependent diabetes mellitus.

Willey 2005 [602]	Primary	4-16yrs	Efficacy of oral or rectal route administered analgesia for post-operative pain.
Williams 2013 [603]	Primary	2-17yrs	Compared cast versus splint for distal radial buckle fractures in children in terms of parental and patient satisfaction, convenience and preference.
Woodgate 2010 [325]	Secondary (Multiple RCTs)	6mth-15yrs	In-depth understanding of Canadian parents' participation in decisions about childhood cancer clinical trials.
Woolfall 2013 [107]	Secondary (Multiple RCTs) MASCOT [575] funding extension application rejected & trial closed prematurely. MENDS [567] POPs [still recruiting] TIPIT [583]	MASCOT: 6-15yrs MENDS: 3-15yrs POP: 4-18yrs TIPIT: < 28wks	Explored how a parent's understanding of a trial might be associated with the way that the trial was explained during the discussion with a practitioner.
Wright 2005 [604]	Primary Recruitment was expected to take 3yrs but took 6yrs.	4-10yrs	Investigated early application hip spica compared with external fixation in paediatric femoral fractures. Recruitment was expected to take 3yrs but took 6yrs.
Wynn 2010 [605]	Secondary Primary paper Wang 2011 [582]	<18mths	In response to slow recruitment study coordinators evaluated factors that affected enrolment and accrual in a sickle cell anaemia RCT.

Young 2006 [606]	Secondary	7-17yrs	Reported results of two studies of social phobia, assessing the extent to which parental reluctance toward medication resulted in pre-treatment attrition in: behavioural, fluoxetine and placebo groups.
Patient Preference Trial or Comprehensive Cohort Design (n=10)			
Cunningham 2011 [584]	Secondary Trial 1: preference group added and trial terminated early due to inadequate sample size.	Adolescents (age not stated)	Reported two RCTs, both terminated early due to inadequate sample size. Trial 1: Multi-centre Orthodontic RCT which compared two different methods of treating a specific type of malocclusion in adolescents. (Trial 2: RCT, no preference data).
Gowers 2010 [607]	Primary	12-18yrs	Compared the clinical effectiveness of inpatient against outpatient treatment and of generalist against specialist management of anorexia nervosa.
Lock 2010 [66]	Primary Trial extended from 5 to 7yrs to increase patient recruitment.	4-15yrs	An embedded qualitative study informed the development of the RCT, it explored patient/parent(s) preferences for different treatment options in patients with recurrent sore throats who had recently been referred to ENT clinic. Extended from 5 to 7yrs to increase patient recruitment.

Mattila 2003 [613]	Primary	≤2yrs	Assessed adenoidectomy in connection with tympanostomy compared with tympanostomy only in preventing otitis media in children.
Paradise 1984 [608]	Primary	3-15yrs	Assessed the efficacy of tonsillectomy and adenoidectomy.
Paradise 1990 [609]	Primary	1-15yrs	Assessed the efficacy of adenoidectomy, comparing surgical and non-surgical management, with equivalent non-randomised preference groups.
Reddihough 1998 [610]	Primary	12-36mths	Compared conductive education (CE) programme with equivalent intensity traditional neurodevelopmental programmes of rehabilitation for young children with Cerebral Palsy.
Rovers 2001 [611]	Primary	9–12mths	Compared ventilation tubes (VT) and watchful waiting (WW) in the management of patients with otitis media with effusion. The generalisability of randomised patients with eligible non-randomised patients was studied via preference groups.
Weinstein 2013 [614]	Primary Preference arms added after 3yrs of recruitment.	10-15yrs	The effectiveness of bracing, compared with observation in preventing progression of the curve to 50 degrees or more in idiopathic scoliosis patients, with equivalent non-randomised preference groups.

Van Wijk 2014 [612]	Secondary Primary paper Van Wijk 2014 [579]	4.5-6.5mths	Primary: Effectiveness of helmet therapy for positional skull deformation compared with the natural course of the condition Secondary: Assess parents' decision for helmet therapy in infants with skull deformation.

**Primary papers were defined as those reporting primary RCT outcome(s). Secondary papers were those reporting embedded/related studies (e.g. qualitative) describing patient/parent experience of trial involvement, reasons for decline, consenting and recruitment.*

4.2.1 Impact of treatment preference on recruitment

Conventional RCTs with randomised treatment groups

Table 4:3 aggregates all descriptive preference data from the included papers. Seventeen papers reported the number of eligible families declining participation because of a preference for treatment, this ranged from 2-50% in conventional trials, [94, 108, 319, 381, 589, 590, 593, 594, 596-601, 604-606] and 4-70% in the two pilot/feasibility phase trials. [586, 587] Eleven RCTs reported the preferences of families who opted for trial participation, [74, 108, 522-526, 588, 591, 602, 603] these treatment preferences were either expressed at enrolment or after randomisation. Five trials reported withdrawal after randomisation. [120, 592, 595, 597, 600] Families either withdrew consent or refused their allocated intervention, but only one of these trials specifically attributed this to a preference for the alternate treatment group. [592]

Patient Preference Trial or Comprehensive Cohort Design

Eight papers (see: Table 4:3) reported RCTs that used non-randomised 'preference groups' in addition to randomised treatment groups from the outset. [66, 579, 607-610, 613, 616] All of these trials reported the number of eligible families declining randomisation groups because of a preference for treatment, this ranged from 11-55%. One of these trials was extended by two years to increase recruitment to randomised trial groups. [66] Two additional trials introduced preference groups because families declined participation because of preferences for treatment. [584, 614]

Treatment preference: Trial design and intervention type

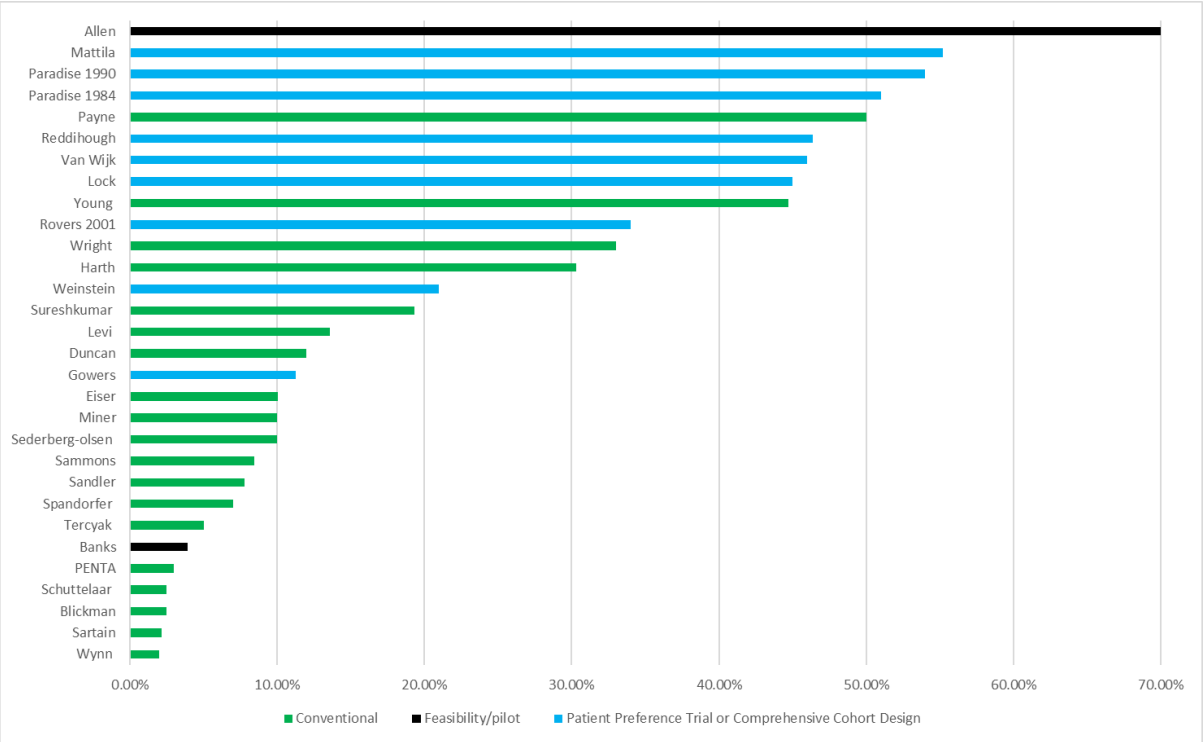
Thirty papers provided figures in relation to the number or percentage of families declining the trial specifically because of preference for treatment (Table 4:3). [66, 94, 108, 319, 381, 585-587, 589, 590, 592-594, 596-601, 604-610, 612-614, 616] RCTs were grouped by trial type, (feasibility/pilot, conventional or patient preference RCT) and graphed in terms of the percentage of participants declining the trial due to preference (see: Figure 4:2). Trials with preference arms were more impacted by preference, with families declining and opting for preference arms. The median number of participants declining RCTs with preference arms was consistently higher (46%) when compared to conventional RCTs without preference arms, (10%) see Table 4:2.

Table 4:2 Median number of families declining randomisation due to preference for treatment

	Number of RCTs*	Total number of participants declining trial due to preference	Mean number of participants declining due to preference	Median number of participants declining due to preference	(%) Median, IQR 25th and 75th percentile	Range % declining due to preference
Pilot/feasibility phase trials	2	13	7	7	(37%) 20-53%	4-70%
Conventional trials	18	875	49	17	(10%) 4-16%	2-50%
Patient preference and comprehensive cohort trials	9	1447	161	133	(46%) 34-51%	11-55%

**29 papers provided data on the number of participants declining due to preference, 1 further paper reported the % declining due to preference. Papers reporting multiple RCTs were excluded from these analyses.*

Figure 4:2 Percentage of families declining randomisation due to preference for treatment: Trial design



Intervention arms perceived to be active or more intense were more consistently preferred in comparison to standard care, usual care, placebo and watchful waiting intervention arms. [74, 96, 97, 107, 109, 323, 526, 531, 586, 588-591, 594, 597, 599, 605, 612-614] However, in some RCTs placebo arms were preferred if parents wanted to avoid antibiotics and medication, particularly when parents were concerned about the side effects of a new drug. [319, 381, 606] Parents considering neonatal RCTs often preferred active treatment arms. [74, 96, 107, 531] There were no consistent findings in relation to preference for more intense treatments in oncology RCTs, [97, 108, 109, 325, 522, 585] those investigating chronic illness, (diabetes and asthma) [319, 525, 526, 591, 601] or RCTs where families considered surgical versus non-surgical interventions. [66, 595, 604, 608, 609, 616]

Table 4:3 Included papers: Aggregated descriptive data relating to treatment preference

Conventional RCTs (n=42)			
Author	**Number of eligible participants consenting to randomisation**	**Number of eligible patients not randomised because of treatment preference n (%)**	**Is preference expressed by patients (in addition to parents)**
Allen 2013	1 (10%) (Feasibility)	7 (70%)	Yes, (only patient preference reported).
Allmark 2010	325 (81%)	Unclear, preference reported qualitatively. [531] ‘30 declined’ ‘45 other reasons’. [569]	n/a neonates.
Banks 2012	76 (50%) (Pilot)	6 (4%)	No.
Barratt 2013	258 (33%)	Not reported. 9 (26%) of non-responders reported concern with being in either the intervention or control group, but only 37/305 non-responders replied to question.	No.

Bauchner 1996	648 (total eligible not reported).	Not reported. Parents were asked their preference at enrolment and 551 (85%) of those randomised preferred single-dose therapy over standard therapy.	n/a children under 6yrs.
Blickman 2013	142 (88%)	4 (2%)	Unclear (patients aged 4yrs+ were asked to complete a standardised study instrument).
Byrne-Davis 2010	521 (71%) [580]	Not reported, preference reported qualitatively. [109] 215 (29%) not randomly assigned: 97 refused, 7 had Down's syndrome, 4 because of toxic effects, 28 other reason, 79 unknown". [580]	No.
Caldwell 2003	Not reported, multiple trials.	Not reported, preference reported qualitatively.	Participant age not stated.
Carvalho 2013	Unclear. 48 'recruited' [120] 44 (100%) 'randomised'. [577]	Not reported, preference reported qualitatively. [120] 3 (7%) parents refused allocated interventions post-randomisation in x 2 trial arms. [577]	No.
Chappuy 2014	Not reported.	Not reported. Some Parents felt that standard treatment was the best group for their child because it was less risky.	Participant age not stated.

Duncan 2004	50 different participants randomised. Total eligible not reported.	8 (between 12-16%)	No.
Eiser 2005	1621 (90%) [576]	181 (10%) declined randomisation (opted for PRED =165, DEXA =16) [576] Preference reported qualitatively,16 (32%) ‘agreed reluctantly to randomisation’. [108]	No.
Forsander 1995	38 (93%)	Not reported. Immediately after randomisation 3 families in the control group reported that they would have preferred the family therapeutic care group.	No.
Glogowska 2001	159 (69 %) [115]	Not reported, preference reported qualitatively. [323] Declined trial in total 70 (31%). [115]	n/a children under 4yrs.

Harth 1990	72 (55%)	40 (30%) of families declined because of ‘concern about side effects of the new drug’ (ketotifen) 60 declined in total.	n/a children under 3yrs.
Hissink Muller 2011	Not reported.	Not reported. 41% participating parents reported a preference for therapy with methotrexate and etanercept and 6% had hoped against assignment to this group. Primary aversion was highest (25%) in the prednisone group. [523] Declined trial n=38 (29%). [574]	No.
Hissink Muller 2012	Not reported.	Not reported. 65% participating parents reported a preference for therapy with etanercept. 5 parents and 2 patients participated in the study to access treatment with etanercept, as initial treatment was not possible nor reimbursed in daily practice.	Yes.

Johnson 2007	Not reported.	Not reported. Participating families stated: Close monitoring group - 27% parents and 70% participants were glad to be in that group. 74% parents and 35% participants sometimes wished they had been assigned the intervention group. Intervention group - 53% parents and 21% participants were glad to be in that group. 25% parents and 47% participants sometimes wished they had been assigned the closely monitored group.	Yes.
Johnson 2009	Not reported.	Not reported. Participating families were blinded to treatment but were asked which treatment group they would have preferred. 60% parents and 53% participants chose the capsule condition. 8% parents and 21% participants chose the no intervention condition. Very few participants and parents (3%) chose the insulin injection condition.	Yes.
Jollye 2009	Not reported, multiple trials.	Not reported, preference reported qualitatively.	n/a neonates.

Levi 2000	Not reported, multiple trials.	Unclear. 3 (14%) stated they declined participation because they felt more comfortable with a “tried and true” method.	No.
Miner 2007	41 (82%)	Unclear. Declined randomised 9 (18%) reasons not reported. After allocation 4 (10%) parents requested that their child receive nebulized fentanyl rather than the assigned IV fentanyl.	No.
Payne 2004	Unclear. Calculated as 322 (69%) of eligible patients. Paper reports recruitment rate of 75%.	59 (50%) ‘Around half of the eligible participants who refused to participate did so because there was a 50% chance of the child being randomised to the inhalational induction arm’.	No.
(PENTA) Paediatric European Network for Treatment of AIDS 1999	197	4 (3%) parents stated explicitly that they were concerned with the use of placebo.	No.

Rovers 2000	187	Not reported. 19 (10%) parents withdrew consent straight after randomisation (15 in ventilation tubes group and 4 in watchful waiting group). 10 (5%) children in the watchful waiting group were treated with ventilation tubes.	n/a children under 2yrs.
Sammons 2007	Unclear. 245 'randomised'. [94] 252 (85%) 'randomised'. [568]	25 (9%) declining families stated they wanted a specific treatment (IV =20 or oral =5). [94] 43 (15%) declined to take part n=6 (2%) excluded post randomisation reasons: 4 withdrawn by parents / 2 by clinician (no further detail provided). [568]	No.
Sandler 2014	78 (87%)	7 (8%) Three did not want to wear headgear for anchorage, three did not want the Nance button palatal arches, but only one patient did not want to take part because he or she was unhappy at "the thought of temporary anchorage devices".	No.
Sartain 2002	399 (86%)	10 (2%) 7 families withdrew from 'hospital care' group because they wanted the 'hospital at home' arm.	Yes.
Schuttelaar 2010	160	4 (2%) Preferred only dermatologist (n = 2), preferred only nurse practitioner (n = 2).	No.

Sederberg-Olsen 1998	429	120 (10%) parents insisted that the child had grommet insertion performed at the time of randomisation.	No.
Shilling 2011	MASCOT: 63 [575] MENDS: 146 (84%) [567] POP: [still recruiting] TIPIT: 153 (57%) [583]	Unclear, preference reported qualitatively. MASCOT Assessed for eligibility (n = 898), Not registered (n = 732), Excluded (n = 103). [575] MENDS 27 (16%) assessed for eligibility but not randomised: ‘declined 11’ ‘other 16’. [567] TIPIT 57 (21%) assessed for eligibility but not randomised: ‘refused’. [583]	Yes.
Snowdon 1997	185 (79%) [573]	Unclear. ‘majority of parents had a keen preference for ECMO treatment group’. Preference reported qualitatively.[74] 48 (21%) were registered but not randomised: 14 died, 19 improved and 15 parents refused trial participation. [573]	n/a neonates.

Spandorfer 2005	73	24 (7%) A further 3 parents refused participation after randomisation to oral rehydration therapy before starting treatment.	n/a children under 3yrs.
Sureshkumar 2012	412 (37%) [381]	214 (19%) Prefer antibiotics 71/ Prefer no antibiotics 143. [381] Primary paper reports patients excluded because 'participation refused by parent' 1935. [571]	No.
Tercyak 1998	56	2 (5%)	Yes (only patient preference reported).
Willey 2005	31	Not reported. 19/31 patients completed a preference questionnaire / 10 (43%) preference for oral, 2 (9%) for suppositories, 7 (30%) no preference / preference for oral more pronounced among girls 5 (83%).	Yes.

Williams 2013	94	Not reported. A significantly larger percentage of parents and patients in the cast group reported that they would not choose the same method of immobilisation again at all time points (baseline, days: 1, 3, 7, 21 after injury).	No.
Woodgate 2010	Not reported. (multiple trials)	Not reported, preference reported qualitatively.	n/a neonates.
Woolfall 2013	MASCOT: 63 [575] MENDS: 146 (84%) [567] POP: [still recruiting] TIPIT: 153 (57%) [583]	Unclear, preference reported qualitatively. MASCOT Assessed for eligibility (n = 898), Not registered (n = 732), Excluded (n = 103). [575] MENDS 27 (16%) assessed for eligibility but not randomised: ‘declined 11’ ‘other 16’. [567] TIPIT 57 (21%) assessed for eligibility but not randomised: ‘refused’. [583]	No.

Wright 2005	108 (46%)	41 (33%)	No.
Wynn 2010	234 (29%)	2% unwilling to take placebo.	n/a children under 2yrs.
Young 2006	Not reported.	125 'Reluctance toward medication treatment accounted for 44.7% of study refusals and was disproportionately common among ethnic minority families.	No.
Patient Preference Trial or Comprehensive Cohort Design (n=10)			
Cunningham 2011	Not reported. (multiple trials)	Not reported. A small number of patients who were eligible declined the trial as they had a treatment preference. These were patients allocated to both intervention groups, so one treatment option was not preferred to the other. Preference arms added.	Unclear.
Gowers 2010	170 (68%)	28 (11%) Not randomised, patient preference.	Yes.

Lock 2010	268 (26%)	286 (28%) declined any follow up, authors assumed that all had a patient preference. 461 (45%) opted for preference groups in cohort.	Only in qualitative sample. Authors did not attempt to differentiate between parent/child preferences in RCT/preference samples.
Mattila 2003	137 (45%)	169 (55%) opted for preference groups.	n/a children under 2yrs.
Paradise 1984	91 (49%)	96 (51%) opted for preference groups.	No.
Paradise 1990	99 (46%)	114 (54%) opted for preference groups.	No.
Reddihough 1998	34 (49%)	32 (46%) declined randomisation.	n/a children under 3yrs.
Rovers 2001	187 (48%)	133 (34%) opted for non-randomised cohort groups. 66 (17%) refused randomisation/follow up via cohort.	n/a children under 1yrs.
Van Wijk 2014	84 (21%)	186 (46%) made decision for treatment.	n/a children under 1yrs.

Weinstein 2013	155 (14%)	228 (21%) opted for preference groups. 297 (27%) declined all follow-up due to preference. 216 (20%) no to randomisation.	No.

4.2.2 Patient or parent preference?

Nine papers explicitly reported the treatment preferences of young people, as well as their parents. [66, 96, 524-526, 586, 597, 601, 602] Child/parental views on preferred treatment groups differed on three occasions. [66, 96, 525] Twelve papers reported findings from trials involving children under the age of six years, so did not include information on the preferences of young people or children. [74, 319, 325, 531, 588, 589, 595, 600, 605, 610, 613, 616] Finally, one trial reported that parents who refused randomisation did so because of "*a desire to have decisional control, and they trusted their physician's choice of treatment more than a computer's choice".* [111]

4.2.3 Health professional preferences for trial treatments

Most studies did not comment on families' reasons for treatment preference, but six papers reported different forms of health professionals' preference for treatment which may have influenced family's preferences. [96, 381, 524, 603, 610, 616] Two trials stated that staff experienced discomfort with children's medication/intervention being selected by a process of randomisation, [96, 610] one highlighted that *"consent was more likely when the recruiting physician was a member of the research team"* [381] and in another, a parent whose child was randomised to a splint treatment group was told the day after randomisation by a clinician outside the RCT that, "*all buckle fractures need to be casted".* [603] These findings suggest that recruiters and treating health professionals may be an important influence on parent and patient treatment preferences when families consider RCT participation.

4.3 Summary of included studies (qualitative data)

Forty papers contained only descriptive data relating to preference, e.g., CONSORT diagram figures for the number of families declining the trial because of a preference for treatment. These papers did not contain qualitative data in the form of parent or participant quotations so were not included in these analyses. Twelve papers contained parent/participant quotations relating to expressions of preference, and data from these papers were synthesised. [66, 74, 96, 97, 107-109, 115, 120, 325, 326, 531] Two of these papers also contained participant quotations, in addition to those of parents. [66, 96] Four papers also investigated the communication practices of families and health professionals at the point of recruitment. [74, 96, 97, 108] Table 4:4 summarises all 12 papers with qualitative data; nine were published in the UK, and one in Canada, Australia and Brazil respectively. Eleven of the included papers were published from the year 2000 onwards (92%).

Table 4:4 Summary: Papers with qualitative data

Publication year / Author	Country	Age range months/years (Participant)	Description of RCT and interventions
1997 Snowdon [74]	UK	Neonates	The ECMO Trial (UK Collaborative trial of extra corporeal membrane oxygenation) compared two methods of life support: conventional management (CM) with oxygenation of the blood via an external circuit (ECMO).
2001 Glogowska [323]	UK	3-4yrs	Speech and Language Therapy: i) immediate treatment: ii) watchful waiting.
2003 Caldwell [97]	Australia	Not stated	Multiple RCTs / research groups involved, including oncology and renal: interventions not defined.
2005 Eiser [108]	UK	4-6yrs	Acute Lymphoblastic Leukaemia (ALL): Drug intervention: dexamethasone and 6-thioguanine compared with agents used in previous trials (prednisolone and 6-mercaptopurine respectively).
2006 Allmark [531]	UK	≥36wks	Total Body Hypothermia (TOBY) trial investigated the use of whole-body cooling for term infants with evidence of perinatal asphyxia and compared intensive care plus total-body cooling for 72 hours with intensive care without cooling.
2009 Jollye [326]	UK	Neonates	Multiple RCTs, non-urgent neonatal: i) Ventilation trial comparing two modes of CPAP ventilation, ii) blood transfusion trial comparing a single infusion to a divided dose 24 h apart, iii) immunoglobulin trial comparing this with a placebo.
2010 Byrne-Davis [109]	UK	2-11yrs	Acute Lymphoblastic Leukaemia (ALL). The trial randomised at 1 of 2 points: Point 1 approximately four weeks after treatment had begun: If child in remission at 28 days but MRD high levels of residual disease i) standard treatment ii) a more intensive treatment. Point 2 approximately 12/13 weeks after treatment had begun: If child in remission at 28 days but MRD low levels of residual disease i) standard treatment (ii) reduced intensity treatment.
2010 Lock [66]	UK	4-15yrs	RCT with preference groups: Recurrent sore throat: i) tonsillectomy and adeno-tonsillectomy, ii) non-surgical conventional medical management.

Publication year / Author	Country	Age range months/years (Participant)	Description of RCT and interventions
2010 Woodgate [325]	Canada	6mth-5yrs	Various trials - individual trial aims not reported. Children were diagnosed with either leukaemia or lymphoma, and 8 had a solid tumour.
2011 Shilling [96]	UK	MASCOT: 6-15yrs MENDS: 3-15yrs POP:4-18yrs TIPIT: Pre-term infants <28wks gestation	MASCOT Management of asthma in school age children on therapy: i) Inhaled fluticasone + placebo tablet, ii) inhaled fluticasone and salmeterol (combined inhaler) + placebo tablet, iii) inhaled fluticasone + montelukast tablet. Funding extension application rejected & trial closed prematurely. MENDS – The use of melatonin in children with neurodevelopmental disorders and impaired sleep: i) Melatonin, ii) placebo. POP – Prevention and treatment of steroid-induced osteopaenia in children and adolescents with rheumatic diseases: i) Risedronate, ii) vitamin D analogue 1-alphahydroxycholecalciferol, iii) placebo. TIPIT - A randomised controlled trial of thyroxine in pre-term infants under 28 weeks' gestation: i) Thyroxine, ii) placebo. Multiple RCTs, all were double blinded.
2013 Carvalho [120]	Brazil	<3yrs	An RCT that compared advanced behaviour management techniques for pediatric dental rehabilitation. Dental Sedation: i) physical restraint, ii) moderate conscious sedation, iii) general anesthesia.
2013 Woolfall [107]	UK	MASCOT: 6-15yrs MENDS: 3-15yrs POP: 4-18yrs TIPIT: Pre-term infants <28wks gestation	See Shilling 2011 for a description of RCTs and interventions.

All 12 papers with qualitative components collected interview data, three collected data via recorded recruitment consultations in addition to interviews, [96, 107, 109] and one study used focus groups in addition to interviews. [97] Four studies collected data during or after the initial recruitment consultation, therefore obtaining parent and patient feedback directly at the point the trial was initially discussed, [96, 107, 109, 120] while the remaining studies asked parents or young people to retrospectively reflect and provide feedback on the recruitment process, or their experience and feelings about the offer of trial participation. Five studies incorporated a constant comparative approach. [96, 97, 107, 109, 325] Three studies drew on thematic analysis, [66, 107, 108] three framework analysis [96, 323, 531] and one paper stated that 'content analysis' was used to develop themes. [120] Two studies did not clearly state which analytic approach was employed. [74, 326] and four did not describe an underpinning approach or epistemological stance. [108, 115, 120, 531]

Six papers presented data collected retrospectively at interviews conducted in the months following randomisation. [66, 74, 97, 108, 323, 326] Three papers presented data from audio-recorded recruitment consultations that happened prior to randomisation, as well as interviews conducted after randomisation. [96, 107, 109] One paper presented preference data collected immediately after informed consent and straight after the randomisation process. [120] Qualitative sample sizes ranged from 7 (families) to 84 participants (mother, father and their participating child). Ninety-two quotations relevant to preference were extracted in total, with a median of six quotations per paper, ranging from 1-17. Table 4:5 describes the study theme(s),

data collection methods and methodological approach of papers included in the qualitative synthesis.

Table 4:5 Qualitative papers: Study theme, data collection and methodological approach

Author/ Published	Number of qualitative participants (parents/ participants)	Study theme(s)	Is preference expressed by patient/parent prior to randomisation?	Data collection method(s)	Approach & data analyses
1997 Snowdon	37 parents: 21 mothers & 16 fathers	Parents' responses to the process of randomisation. Detailed exploration of parental reactions to random allocation of treatment in a neonatal RCT.	No - retrospective report of preference from RCT parents	In-depth interviews: in 16 interviews both parents were present & in 5 only mothers were involved.	Analytic approach not stated / 'Textual analysis using Atlas-ti'
2001 Glogowska	20 parents	Reported attitudes of parents whose child was invited to take part in an RCT.	No - retrospective report of preference from RCT parents and non-trial parents	In-depth semi-structured interviews	Framework analysis
2003 Caldwell	33 parents: 29 mothers & 4 fathers	Explored parents' attitudes to children's participation in trials, identifying factors that influenced decision-making and perceived risks and benefits. Multiple trials, oncology and renal & parents of healthy children.	No - retrospective report of preference from RCT parents and non-trial parents	4 Focus groups and 5 individual interviews	Constant comparative / thematic analysis
2005 Eiser	50 mothers	Mothers' (of children newly diagnosed with Acute Lymphoblastic Leukaemia) views regarding consent to randomised controlled trials.	No - retrospective report of preference from RCT parents and refusers	Semi-structured interviews	Thematic analysis
2006 Allmark	30 sets of parents	To assess whether continuous consent, a process in which information is given to research participants at different stages in a trial, and clinician training in that process were effective when used by clinicians while gaining consent to the TOBY trial.	No - retrospective report of preference from RCT parents and refusers	Semi-structured interviews	Framework analysis

2009 Jollye	7 families	Explored the thoughts and feelings of parents in their decision-making process, either choosing or declining to participate in neonatal clinical trials.	No - retrospective report of preference from RCT parents and non-trial parents	Semi-structured interviews - 2 months after baby discharged home	Analytic approach not stated: 'Analysed using an open coding mechanism similar to that described by Cresswell 1998'.
2010 Byrne-Davis	30 parents: 17 mothers & 13 fathers	Examined how recruitment looked to an observer and how it felt to parents, (of children with low-risk acute lymphoblastic leukaemia) to identify how doctors' communication could promote or inhibit optimal recruitment.	Yes - trial recruitment consultations were matched with retrospective interview data	Audio-recorded recruitment consultations & semi-structured interviews	Constant comparative
2010 Lock	12 families: mothers & young people	An embedded qualitative study which informed the development of the RCT. Investigated families' experiences of recurrent sore throat and their preferences for different treatment options.	No – families participating in a nested qualitative study reported preference when interviews were undertaken to inform the development of the RCT	joint semi-structured interviews with parent/child	Iterative thematic analysis

2010 Woodgate	31 parents: 20 mothers & 11 fathers	In-depth understanding of parents' participation in decisions about childhood cancer clinical trials.	No - retrospective report of preference from RCT parents	In-depth interviews: Twenty parents from 10 of the families interviewed as couples, parents from the remaining 20 families (mothers n = 20, father n = 1) took part in individual interviews.	Constant comparative
2011 Shilling	Interviews: 84 members of 60 families. 58 mothers, 4 fathers and 22 young people.	Communication about trials as observed and experienced & factors that influence decision-making. Aimed to identify strategies to improve recruitment and trial conduct, by comparing practitioners' and parents' accounts of the invitation to enter a child into clinical trial.	Yes - trial recruitment consultations were matched with retrospective interview data	Audio-recorded recruitment consultations & semi-structured interviews	Constant comparative / framework analysis
2013 Carvalho	15 mothers	The understanding and perceptions of mothers regarding the informed consent and randomisation processes. It was assumed that mothers would have difficulties understanding the consent form and that most would accept randomisation because their children needed dental treatment.	Yes - after the informed consent process	Interviews in two phases: 1. After a parent had signed the consent form: 2. After the randomisation process.	Content analysis was used to develop 'themes'
2013 Woolfall	41 families (with a matched recruitment discussion and interview)	Explored how a parent's understanding of a trial might be associated with the way that the trial was explained during the discussion with a practitioner.	Yes - trial recruitment consultations were matched with retrospective interview data	Audio-recorded recruitment consultations & semi-structured interviews.	Constant comparative modified to fit with criterion of catalytic validity / thematic analysis

4.3.1 Critical appraisal

CASP scores are shown in Table 4:6. Five papers which each scored six points were included in a sensitivity analysis to assess whether synthesised data changed significantly if they were removed. [74, 108, 323, 326, 531] This was not the case, and since none of the papers were deemed to be ‘fatally flawed’ [617] and unsuitable for inclusion, all assessed papers were included in the final synthesis. The most frequent areas of weakness included lack of transparency in reporting of: data analysis methodology, ethical issues, and reflexivity. However, there is a lack of consensus around quality assessment criteria and the way in which this is applied to qualitative studies. [533, 534, 538, 539, 618]

Table 4:6 CASP scores and distribution of third order constructs

Studies which supported the development of 3rd order constructs	CASP score 0-10 <6 indicates weaker quality study	Third order construct one Making sense and asking questions about the RCT		Third order construct two Motivations and reservations about taking part in an RCT					Third order construct three An emotional response to randomisation				
		1.1 Understanding of trial processes (nature of RCT, randomisation, equipoise)	1.2 Understanding of treatment arms and unanswered questions (Assimilating new information with pre-existing knowledge)	2.1 Perceived benefit	2.1 Perceived risk	2.2 Access to treatment (medication or therapy)	2.3 Management of condition & practical implications	2.4 A difficult decision	3.1 Hopes and fears	3.2 Vulnerability and responsibility	3.3 Fate and Luck	3.4 Disappointment and relief	3.5 Anger and happiness
Carvalho 2013	9	✓	✓	✓		✓		✓	✓	✓	✓	✓	
Woolfall 2013	9	✓	✓	✓		✓			✓				
Shilling 2011	9	✓	✓	✓		✓			✓		✓		
Lock 2010	9			✓		✓	✓					✓	
Byrne-Davis 2010	8	✓	✓	✓	✓			✓	✓			✓	
Caldwell 2003	8		✓	✓	✓	✓		✓	✓	✓		✓	✓
Woodgate 2010	7	✓	✓		✓		✓	✓	✓	✓			
Jollye 2009	6	✓	✓	✓	✓				✓	✓			
Allmark 2006	6	✓	✓									✓	✓
Eiser 2005	6	✓	✓	✓		✓		✓		✓		✓	
Glogowska 2001	6	✓	✓	✓		✓			✓	✓	✓	✓	
Snowdon 1997	6	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓

4.3.2 Synthesis of Qualitative data: Meta-ethnography

Data from the 12 original papers were translated into each other to form a synthesised translation made up of three overarching (third order) constructs, consisting of eleven inter-linked sub-themes from parent data, and eight interlinked sub-themes from patient data (see: Section 4.3.6 The preferences of children and young people). Appendix 2 provides the translation of all first, (quotations) second, (authors' themes) to third order (synthesised) constructs.

Synthesis of treatment preference data

Only one of the original papers included in this meta-ethnography explicitly referred to preference as a named theme in the primary data analysis: 'Preference for different arms of the trial'.[108] However, treatment preferences were expressed in several data extracts, and five further papers discussed preference for treatment within other themes of their analyses or discussion sections. [66, 74, 97, 109, 325] Six authors discussed equipoise, [66, 74, 96, 97, 109, 323] but only one explicitly used the term 'equipoise' in a heading outlining a key finding: 'Parents appeared to understand equipoise, voluntariness and randomisation'. [109]

Parents' preferences for treatment were identified in all 12 papers, but only two papers included in this synthesis reported the views of young people in relation to preference for treatment and trial participation, [66, 96] (see: section 4.3.6 The preferences of children and young people). One paper demonstrated that parents and young people can have different preferences for treatments offered in an RCT,

in this case parents overwhelmingly preferred surgery and young people a non-surgical intervention. [66]

Line of argument parent data: Doing the best for my child

Table 4:7 displays the third-order constructs, inter-linked sub-themes and line of argument developed from parental data. There was considerable overlap between each overarching third order construct, and the sub-themes within them. Parents' understanding of trial processes (e.g., randomisation and equipoise) influenced their motivations and reservations about their child's participation (e.g., perceived benefits and risks). Some parents were emotional in the run up to randomisation, when provided with information of their child's allocated treatment group, or when recalling aspects of the recruitment consultation (e.g. the responsibility they felt when making the decision to participate). Parental emotion ranged from happiness to disappointment, and parents demonstrated a vulnerability to the randomisation process that includes hopes, fears, anger and relief. A new interpretation of the data, an expression of the synthesis, was taken forward as the line of argument: 'Doing the best for my child'. Parents not only engaged in 'sense making' work in relation to trial processes, they also engaged in 'moral identity' work as they juggled 'sense making' and the principle of 'altruistically' helping to progress medical research for future young patients, with the competing demands of being a good parent and making the best decision for their child.

Table 4:7 Parents' data: Third-order constructs, inter-linked sub-themes and line of argument

Third-order constructs and inter-linked sub-themes	Line of argument
1. Parents' preferences for treatment: expressed while making sense and asking questions about the RCT 1.1 Understanding of trial processes (nature of RCT, randomisation, equipoise) 1.2 Understanding of treatment groups and unanswered questions (Assimilating new information with pre-existing knowledge)	**Doing the best for my child**
2. Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT 2.1 Perceived benefits and risks (facilitators and barriers to trial participation) 2.2 Access to treatment (medication or therapy) 2.3 Management of condition and practical implications 2.4 A difficult decision	
3. An emotional response to randomisation and expressions of preference for treatment 3.1 Hopes and fears 3.2 Vulnerability and responsibility 3.3 Fate and luck 3.4 Disappointment and relief 3.5 Anger and happiness	

4.3.3 Parents' preferences for treatment: expressed while making sense and asking questions about the RCT

A minority of parents understood trial aims and rationale for randomisation. These families also appeared to be in a place of equipoise about trial treatments and preferences were not expressed:

> *"that's the thing with the randomisations they don't have the figures at the moment to say well yes this regime does work better than this regime" [Byrne-Davis]*

> *"treatment is excellent anyway and anything they offer [in the trial] can only be better" [Eiser]*

One parent highlighted the importance of being treated as capable of understanding trial processes, (such as placebo) and having information provided in a way that was accessible. This was developed in the line of argument as the way in which parents assimilated new information with their pre-existing knowledge of RCT research:

> *"if it is explained to people...you are more likely to get a positive sort of response […] if...I didn't know anything at all about trials, I'd be thinking trials to me sound experimental, placebo to me sounds like it's not a real drug. ...it all depends on how it's been worded and how it's been explained..." [Caldwell]*

Some parents questioned equipoise when trial groups delivered either 'standard' or 'high intensity' treatment. These families expressed preference because their "*gut reaction*" was to *"give him more chemotherapy". [Byrne-Davis]* Parents were

assimilating new information into their pre-existing cultural or personal knowledge of treating a known condition e.g. cancer. Another family also found it difficult to let go of their initial preference for ‘high intensity’ treatment, and struggled with the concept of equipoise:

> *“very difficult for me to say, yes, he could just have one [intensive block]” [Byrne-Davis]*

> *“in the back of my mind I can’t let go of the thought that two intensive periods is better than one” [Byrne-Davis]*

Some families confused eligibility for the RCT with eligibility for their preferred trial treatment:

> *"anybody eligible for it should use it [ECMO]" [Snowdon]*

Expressions of preferences were sometime subtle before randomisation and group allocation:

> *“Oh, fear of what I want not happening”*
>
> *[said by a mother while waiting for randomisation: Carvalho]*

The majority of parents described misunderstandings about trial processes, particularly the ‘reasons’ for using a process of randomisation to determine treatment. Parents correctly understood the ‘end result’ of randomisation, that their child has a 50/50 chance of receiving one treatment group or the other. However,

there was often a lack of understanding ‘why’ this process was used. Parents lacked equipoise and felt there was a ‘right’ treatment group, which would be more effective. Parents involved with trials that had a watchful-waiting group, or placebo found it particularly difficult to understand the rationale and legitimacy for use of a placebo group:

> *“[placebo group] that’s just like going to the doctor and them saying well we are just not going to treat this child” [Caldwell]*

> *“I was told yes, he had a problem and he needed help and I think now, well, I’ve got to wait ... to get any help” [Glogowska]*

> *“What my question is, if they say he’s gonna take the placebo… the dummy one what is he going to benefit from the study?” [Shilling]*

Parents also assigned their own ‘rationale’ for randomisation, because of ‘cutbacks’ not because of uncertainty about treatment effectiveness:

> *“It was a case of if his name came out of the box ... then he was lucky enough to go on it [active therapy as opposed to watchful waiting] which I think is wrong ... but then I suppose it’s all the cutbacks” [Glogowska]*

Expressions of preference were frequent during interviews with families who had consented to trial participation, suggesting that these families decided to participant despite preference for treatment. This was often the case where trial treatment was unavailable outside of the RCT:

"I remember saying to him… 'Oh great, great, like some effing placebo' is what I said to him… so, no, I totally understood that idea, [randomisation] so I was kind of glad" [because baby received preferred 'active' treatment] [Allmark]

"We were disappointed. You go through all that talking and decision-making and then you get the old treatment anyway" [Eiser]

Some parents believed that the only way to access a preferred treatment for their child was via trial participation:

"in order to get that tablet he has to participate in the trial" [Shilling]

"I was just thinking I hope he gets the [trial drug] one'' [Woolfall]

In one study [120] it was unclear whether all the interventions offered via the RCT were available to families outside the trial. In this study most parents (all but two) accepted the randomised allocation despite nine having expressed that they would have chosen one of the other trial interventions for their child when they were asked before randomisation:

"We would like to have gotten the general anesthesia . . . now we have to do it with the sheet" [Mother's expectation before randomisation, general anesthesia. Group assigned, physical restraint] [Carvalho]

"Oh, no!" [Mother's expectation before randomisation, physical restraint. Group assigned, general anesthesia] [Carvalho]

"Oh, I would not want [to do it]. I came here with my heart in my hand thinking about it. I thought I could choose to come here and say 'I do not want general anesthesia.' The doctor at the health center had already said that a sedative might be necessary, so I was already thinking 'I will not allow it.'" [Mother's expectation before randomisation, physical restraint. Group assigned, general anesthesia] [Carvalho]

Although some parents had preferences for a specific trial group, upon randomisation to their non-preferred group they made altruistic comments about 'helping others':

"We would have wanted the old one [drug] but if it helps others it's Okay. They pick you at random and we got picked [for the new drug]" [Eiser]

"Maybe he might get [the trial drug], maybe he mightn't. Maybe, if he does get it, it might help him in some way and if he doesn't get it then, you know, at least I tried to help [you] with the study" [Shilling]

Some parents incorrectly believed that their child was randomised to a treatment because the process of randomisation considered 'factors' about their child's condition and/or circumstances, which resulted in randomisation to a specific treatment, (therapeutic misconception). When a minimal residual disease test result came back as 'higher risk' a parent believed this was the reason why her child was randomised to regimen C rather than staying on regimen A. This mother expressed a preference for the allocated treatment because, "*the treatment's going to step up a*

bit hopefully to [...] get the leukaemia under control" [Byrne-Davis]. Parents felt their child was receiving the 'right' treatment for their specific needs via RCT participation:

> *"If she'd [the therapist] seen something ... and thought ... this is something really serious well then he wouldn't have been put on that sort of waiting group" [Glogowska]*

> *"I thought that the doctor had entered Timothy for the trial as he was perfect for the ECMO treatment" [Snowdon]*

A lack of understanding about RCT eligibility criteria also resulted in the perception that treatment had been chosen completely 'randomly' with no specified criteria:

> *"the computer makes the decision [...] and I just think, they give you all this information and then, you know, randomisation is just purely you're picked at random, it's a lottery. […] I think they should have certain criteria, that maybe if you fit these specific criteria's, or if you have a daughter that's fifteen years of age, or twelve years or whatever, a reason for not going on it would probably be better rather than just saying 'oh well, the computer picks and that's it.'" [Byrne-Davis]*

Parents' potential misperceptions of trial processes appeared very logical when analysed with data from recorded conversations of recruitment consultations. [96] In the extract below a recruiter is trying to explain that *specific* trial drugs would be assigned by a process of randomisation. During a later interview this parent explained that they had understood this to mean that trial drugs would be *selected* randomly:

Doctor: And by randomised, what we mean is that we just randomly pick one. So it's almost like a sort of, it's usually a computer program that just sort of.

Parent: A lucky dip?

Doctor: Yeah it is exactly like that. Like a lucky dip […] so it's almost like just, you know, saying well we just picked this out of a hat and [your son] got this treatment"

Recruitment consultation [Shilling]

"A bit wary, […] because I thought, 'Oh what's, just going to give him some random tablets or anything'"

Interview [Shilling]

Another mother declined participation because she simply "*switched off*" after the doctor first mentioned the way that drugs would be administered to her baby in the RCT:

Doctor: The hormone is given through err … an infusion. It's called err a syringe pump basically, which is, you know, puts medicine to the veins. Um and we will give it once a day

Mother: Okay

Doctor: All these procedures won't cause distress to your baby […] if your baby is not getting fully milk feeds, then we will use the lines. Once a baby is going on to full or milk feeds, then we will give drops and things […] so it won't cause any distress

Recruitment consultation [Shilling]

"[Doctor] told me, I think, they're going to put like kind of a small tube inside him, so […] I remember after that, I just hated this idea of the tubes were going to go in! So I don't remember why they was putting the tube. I think they were studying something, but I just, I just didn't like the idea from the beginning so I didn't give it more attention" [mother declined RCT]

Interview [Shilling]

Where available, recruitment consultations also highlighted the way in which parents' lack of equipoise about treatment groups might be subtly reinforced via the language used by clinicians during recruitment consultations:

"So we are running this study for the last year now, where I'm afraid half the [babies] get the supplement and half the [babies] doesn't get it" [Shilling]

Some parents still had 'unanswered' questions after their child had been randomised, questions focused on treatment and associated risks:

"is there a risk of death?" [Mother's expectation before randomisation, general anesthesia. Group assigned, general anesthesia] [Carvalho]

"he [the doctor] was saying, you know "you've got to balance out the low risk here to the high intensity here". Does that balance out? And with her having the [name of serious infection], um, do we really want to put her at risk from being susceptible to those sort of things again when, maybe, she doesn't really - in the bracket that she's in, where it is a 85%, 95% cure rate - do we need to put her in that thing?" [Byrne-Davis]

4.3.4 Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT

Parents participating in 10 studies discussed the ways in which their children might benefit from participation in the RCT. Benefit was sometimes linked to gaining access to a preferred treatment, with parents feeling that one treatment group was better than the other:

> *"They might get the new drugs that work.." [Caldwell]*

> *"I just felt there could have been ten other babies with exactly the same problems as him and now there is nine sets of parents who are now being told that their baby's not being accepted onto the trial [conventional management]. And I did feel a bout of guilt for that but I could have gone out and...danced on water...when I got told that he'd been accepted [ECMO]" [Snowdon]*

Some parents were aware that they could access RCT interventions outside the trial and decided before randomisation, if their child was not randomised to the '*right*' group they would request the treatment they perceived as '*right*' for their child. The 'right' treatment group was often perceived as 'active', 'new' or 'more aggressive', as opposed to 'inactive' 'old' or 'standard':

> *"I couldn't justify saying O.K. we'll go along with this research group [watchful waiting] and wait for a year because he needed help then" [family crossed-over] [Glogowska]*

"I'd heard about [trial drug] and I'd read a few things on the internet, because of [child's name's] sleeping, and I just thought, right I'm going to ask if he can have it'' [Woolfall]

"He would be peeved off if he got the jelly beans...[placebo] he would want the real thing..." [Caldwell]

Families accepted allocation to a 'placebo' or 'old' treatment in the short term, because their child would then be able to access the 'real' or 'new' treatment at the end of the trial:

"I was at the end of my rope...if it was the placebo, well that means that we can try the real thing anyway [at the end of the trial]" [Caldwell]

"We were glad to get the old treatment. It means if she relapses we can still have the new treatment [at the end of the trial]" [Eiser]

Parents also believed that access to *any* treatment, or their *preferred* treatment was only possible via the RCT, even when medication was available outside the trial:

"It cannot continue the way it is. I am like really afraid of general anesthesia, but, as others say, if it is necessary, what can I do? . . . As I am receiving the treatment for free I accept what we get. And I have no choice" [Carvalho]

"I didn't see why I […] could say 'no' to it. Because I thought, well it's, you know, a 50/50 chance of her getting […] this additional help which she might need" [Shilling]

''I've got sort of a 50/50 chance of either she gets the drug or she gets the placebo. But she wouldn't be getting it [drug] otherwise'' [Woolfall]

Access to treatment and potential benefit were closely balanced with consideration of risk and possible deterioration. Some families also mentioned 'risk' in their discussion of preference for treatment. Although more aggressive treatments were more often preferred, less aggressive treatments were accepted as an alternative because of the benefit of lower risk:

"we were slightly disappointed that [...] he got regimen A but of course the flip side of the coin is if he gets away with it… and he avoids a much more toxic regimen… then fantastic" [Byrne-Davis]

Some parents worried about making a decision that might result in their child being allocated to a treatment group that proves to be less effective in the long term:

"it's a worry thinking you're doing the wrong thing...people don't want to...(be) the one being responsible once again" [Caldwell]

''what if Anna is put on (one group of trial) and things didn't work out as well…would it have made a difference if Anna had the other type?'' [Jollye]

In two papers parents discussed preference in the context of decision-making and the ongoing day-by-day or long-term management of their child's condition, in very contrasting medical conditions, childhood cancer and re-current sore throat. [66, 325] In the context of cancer treatment, preference was only hinted, parents reported having to live with the decision they had made (to opt for trial participation), with the anticipation of managing the condition via an assigned treatment regime perceived as 'difficult'. These views were taken forward in the line of argument as 'a difficult decision':

> *"I'm sure if he had been chosen for any other arm except for the difficult one, I would not have given it another great thought. But it all came down to the fact that he got chosen for the one with so much more intravenous and lumbar puncture medication, then it threw me for a loop and I went through a very tough period. Not the initial period because you have 56 days before you get randomized. So you have a long time before you get randomized" [Woodgate]*

Parents expressed preferences for surgical treatment for recurrent sore throat, because of prior positive experience of this approach, and to minimise the long-term impact the illness was having in terms of pain, discomfort and school attendance:

> *"Yeah his brother had his took out and he's been brilliant since he got his done … it was the best thing I could have done for him … that's why we are trying to push to get his done because it's just recurring all the time, every couple of months or so and it's not fair on the bairn and it's not fair on his education either because he's having to have the time off school because he's just, well he wouldn't be any good at school" [Lock]*

"If it come to the 10 month up and he didn't need it done, my wife says, 'Oh I might get it done anyway, just in case" (Father of 07, male, age 7) [Lock]

4.3.5 An emotional response to randomisation and expressions of preference for treatment

Some parents experienced the offer of treatment for their child, via a process of randomisation as an emotional decision. This was apparent in the language used by parents when describing the time leading up to randomisation, or the retrospective accounts of their response to being informed of the group their child had been allocated via randomisation:

"I came here [day of randomisation] with my heart in my hand thinking about it…" [Carvalho]

"But the minute that it hit me full in the face was when we got chosen for the tough arm that hit me like a lead brick" [Woodgate]

"unfair" "hard" "tough" [Snowdon]

Emotional responses to randomisation included disappointment, fear or anger when a child was randomised to what was perceived as 'the wrong' or an ineffective 'placebo' group. Expressions of relief, and in some cases, exhilaration were apparent when the outcome of randomisation was a preferred treatment:

“we were slightly disappointed that [...] he got regimen A” [Byrne-Davis]

“We were disappointed. You go through all that talking and decision-making and then you get the old treatment anyway” [Eiser]

"We went back to the ward. The nurses said "Oh, he hasn't got the ECMO, he's staying here" and them saying that we thought, oh dear, you know, we've had the wrong one or something. We felt disappointed" [Snowdon]

“then he was lucky enough to go on it” [immediate treatment group] [Glogowska]

“Relieved. I feel like jumping for joy. That is great” [kisses child] [laughs] [Carvalho]

In the context of a highly stressful situation, when parents had been told their new-born child’s life was in danger, one parent could not recall being told about the use of randomisation in the trial. This parent had a clear ‘preference’, or perception that one treatment in the trial (ECMO) was more effective than the alternative trial treatment, which their child had already received and showed no improvement. In retrospect, this parent stated that having an understanding that treatment would be decided via the process of randomisation would have been highly problematic for them:

"It probably would have killed me if I had known that it was a randomized test and if they had turned around and said she couldn't go on, [ECMO] ...because I knew the ventilator wasn't helping her which meant...as good as 'I am sorry there is nothing else we can do but wait for her to die'" [Snowdon]

Some parents felt that they had nothing to lose by entering the trial because it gave a 50% opportunity of getting 'additional help'. Others felt they could not decline the trial and opt for their preferred treatment because it was not available 'for free' outside the trial:

"I didn't see why I […] could say 'no' to it. Because I thought, well it's, you know, a 50/50 chance of her getting […] this additional help which she might need" [Shilling]

"As I am receiving the treatment for free I accept what we get. And I have no choice" [Carvalho]

Some parents questioned the ethical basis of randomisation when one treatment group was perceived as more effective than another. For example, ECMO treatment [74] was already used in the USA despite not having been compared with standard care via a trial. This was particularly apparent where trials were recruiting children who were already in pain, or facing a life-threatening condition:

"who gives them the right to play God with babies lives?" [Snowdon]

“why the hell have we got it on trial when it's been in the States and it's got an 89% success rate or whatever?” [Snowdon]

Placebo treatment was perceived as ‘no treatment’ with a lack of apparent understanding about why a placebo was being used as a comparator:

“[placebo] that’s just like going to the doctor and them saying well we are just not going to treat this child” [Caldwell]

Preferences were described in terms of hopes and fears, hope for the treatment perceived to be ‘*better*’ and fear of getting a treatment that the parent was ‘*afraid*’ of in terms of the consequences of procedures (such as anaesthetic) involved in the process of getting the necessary treatment that their child required:

“if there was a hope that he would get better treatment then at least we felt like we’d done everything that we could” [Byrne Davis]

“It cannot continue the way it is. I am like really afraid of general anaesthesia, but, as others say, if it is necessary, what can I do?” [Carvalho]

Parents understandably experienced a strong sense of responsibility about making the ‘right’ decision for their child. This highlights parents’ vulnerability to the randomisation process because of the preferences which they held:

"She [the doctor) said had it been her child and this was chosen (standard treatment) for him probably she would do exactly as I am doing, and that

was enough to make me calm...She too agreed with what I'm saying and feels that it's a wise decision. That was enough to make me at peace again. And now whatever happens with [name of child's] treatment… relapse or whatever, I will never look back and say I've made a poor decision. I will not do that" [Woodgate]

"it's a worry thinking you're doing the wrong thing...people don't want to...(be) the one being responsible once again." [Caldwell]

This emotional response related not only to parents' preferences for a specific trial group and the fact that they were focused upon 'doing the best' for their child, but also in relation to parents' vulnerability, since feelings of nervousness, regret and guilt were often discussed in relation to the decision to proceed with randomisation. Some parents responded to this vulnerability by discussing 'fate' and 'luck' in relation to the outcome of randomisation, despite having preferences for treatment:

"I tell you it's kind of going through [your] whole life without following religion or anything like that but at that time you cling on to anything really and I thought there is only one decision here and it has to be Fate... He stayed and had traditional treatment and the fact that he didn't go to the ECMO as far as I'm concerned the decision was right. Fate played its hand" [Snowdon]

"I have talked to God because He knows what is best for him, doesn't He?" [Carvalho]

"it was a case of if his name came out of the box ... then he was lucky enough to go on it ..." [Glogowska]

4.3.6 The preferences of children and young people

Line of argument patient data: Wanting to get better and help others

Fewer data were available to provide a comprehensive translation of young peoples' expressions of preference for treatment, but young people also engaged in their own 'sense making' work in relation to trial processes, (such as randomisation) and access to treatment. Young people expressed overt preferences for treatment on two occasions, in two of the twelve papers. [66, 96] Both participants expressed a preference for 'active' treatment:

"I was thinking, this could be really good for me but what if it's the placebo then, um, it's like I'm doing it for nothing basically" [11–14 years] [shilling]

"I was a bit disappointed actually because I just wanted to get rid of it [sore throat] straight away" [randomised to non-surgical conventional medical management, 15-year-old-female] [Lock]

One of these studies reported *'substantial differences between children and their parents' [66] [pg.34]* in relation to preferences for non-operative or a surgical intervention for the management of recurrent sore throat:

Lock: However, it must be made clear here that there were substantial differences between children and their parent(s) regarding their views on surgery. On only three occasions were parent(s) and child in agreement regarding their desire, or lack of desire, to have surgery. On two other occasions the child exhibited a strong desire

for surgery while their parent(s) was less sure; these were the two oldest children in the sample. In all other cases it was the parent(s) who desired surgery while the child was either 'worried', 'scared', 'panicked' or adamant that they did not want surgery. [66] [pg.34]

Four further quotations from young people related to other concepts discussed by parents, such as perceived personal benefit, but also the potential to help others presented with a similar situation in the future. Although these are not direct expressions of treatment preference, they did demonstrate that young people understood that different treatment options were available in the trial, and that there was unpredictability in terms of treatment and the long-term management of their condition:

> *"They basically said that some people would get the real thing and others needed to get the placebo" [11–14 years] [Shilling]*

> *"You just think like 'oh […] what are we gonna have to do' like, 'what medicines are we gonna take' and then obviously […] 'what will happen as a consequence of the medicine'" [11–14 years] [Shilling]*

> *"Even though one of them might not work for the bones [?placebo?] and things will it do some good for me?" [11–14 years] [Shilling]*

> *"It would benefit me and other children in the future for like if they have the same thing they can get medicine and not have to do the study but like get it straight away because I helped" [11–14 years] [Shilling]*

Young people wanted to help other young patients in the future, but also wanted to facilitate their own recovery via RCT participation. One young person understood that there was unpredictability in terms of treatments available in the RCT, and two contemplated how their assigned treatment might impact the long-term management of their condition. A new interpretation of young peoples' preference data was taken forward as the line of argument: Wanting to get better and help others. Table 4:8 displays the third-order constructs, inter-linked sub-themes and line of argument developed from patient data.

Table 4:8 Young peoples' data: Third-order constructs, inter-linked sub-themes and line of argument

Third-order constructs and inter-linked sub-themes	Line of argument
1. Participants' preferences for treatment: expressed while making sense and asking questions about the RCT 1.1 Understanding of trial processes (nature of RCT, randomisation, equipoise) 1.2 Understanding of treatment groups and unanswered questions (Assimilating new information with pre-existing knowledge)	**Wanting to get better and help others**
2. Participants' preferences for treatment: expressed motivations and reservations about taking part in an RCT 2.1 Perceived benefits and risks (facilitators and barriers to trial participation) 2.2 Access to treatment (medication or therapy) 2.3 Management of condition and practical implications	
3. An emotional response to randomisation and expressions of preference for treatment 3.1 Hopes and fears 3.2 Disappointment 3.3 Altruism versus personal benefit	

4.4 Discussion: Systematic literature review and qualitative synthesis

This is the first systematic review specifically investigating whether treatment preference influences recruitment into paediatric trials. This systematic review identifies that families often have preferences for treatment at recruitment, and some families consent to trial involvement despite having preferences for a specific treatment. Reports of preferences for treatment ranged widely in feasibility RCTs, (4-70%) conventional RCTs, (2-50%) and in trials with preference groups (11-55%). Declining accrual rates and a loss of clinical equipoise led to the closure of two trials [584, 600] and two required extensions because of slow recruitment. [66, 604] Whilst several trials introduced preference groups to improve recruitment, this design can have disadvantages such as extended trial duration to meet recruitment targets and reducing external validity and generalisability of results. [288, 619]

Synthesis of data from 12 papers drew on meta-ethnographic techniques, and three overarching third-order constructs were developed from these data which were taken forward as the line of argument: ‘Doing the best for my child’ and ‘Wanting to get better and help others’. Parents’ preferences for treatment were expressed while: making sense and asking questions about the RCTs, as motivations and reservations about taking part in the RCTs, and at times parents expressed an emotional response to randomisation, which was linked to preference for treatment. [66, 74, 96, 97, 107-109, 120, 323, 325, 326, 531] Only two papers included data relating to young people’s preference for treatment. [66, 96] Young people were primarily concerned with their own recovery, but also demonstrated an

understanding of the principle of ‘altruistically’ helping other young patients in the future.

Strengths and limitations

A key strength of this review is its breadth, a comprehensive number of paediatric RCT papers were screened for inclusion by two reviewers at all stages in the review process. The review was enriched via the inclusion of a wide range of paediatric conditions, trial contexts, recruiting paediatric participants of all ages. This review also included data from secondary papers reporting recruitment issues, and primary main trial papers were scrutinised, incorporating data that was reported using CONSORT guidelines. [620, 621] Synthesis of qualitative data drew on meta-ethnographic techniques and provided an in-depth understanding of the way in which preferences for treatment are discussed by parents (and young people) in a wide range of trial contexts. It also identified preference related issues that were important to parents’ decision-making, e.g. perceived benefits and risks, access to treatment, and highlighted the vulnerability and responsibility that parents often feel when considering trial participation for their child.

Seven papers in this review reported findings from multiple trials in one paper, [96, 97, 107, 325, 326, 584, 585] and many of the secondary papers did not report full CONSORT flow diagrams, therefore those who were lost to follow-up or withdrew due to preference could not be reported. This systematic review was unable to describe or analyse the effects of preference for treatment on retention or the outcomes under investigation in paediatric trials, (due to time limitations) and these areas require further investigation in the future. If trial acronyms or references were

provided in secondary papers a search was carried out for each related primary paper, but only 18/28 additional papers were located. Data relating to 'participant flow and recruitment' was not always reported consistently in 'primary' RCT papers. The 40 papers reporting descriptive preference data were not appraised using The Cochrane Collaboration's tool for assessing risk of bias. [8] Although this might be considered a limitation of this systematic review, the review did not analyse or compare data statistically across studies – this would have been impossible due to the heterogeneity of included papers.

The 12 papers that provided data for the qualitative synthesis (meta-ethnography) reported findings from a wider range of trial contexts and paediatric conditions. [66, 74, 96, 97, 107-109, 120, 323, 325, 326, 531] However, the included papers had very different research aims and objectives, none of which specifically focused on identifying preferences for treatment. Although the qualitative synthesis developed a line of argument, accounting for 'preference' related issues across the 12 papers, inevitably some of the complexity and wider analyses carried out by the first authors was not reflected in the synthesised data. For example, Shilling et al reported that *'Some parents viewed the trial approach as a positive or exciting opportunity'* [96] [pg. 69] and this finding was not reflected in the synthesised 'preference' data (e.g. An emotional response to randomisation: A difficult decision). However, every effort was made to carefully consider all themes, and the complexity of data reported and discussed by the first authors when carrying out the data synthesis.

Links to previous literature

Hope that their child would benefit from trial interventions, [94, 270, 307, 308, 310, 315-320] and gaining access to interventions that might not otherwise be available [93, 120] were motivating factors for parents discussing trial participation, and these factors influences parents' preferences for interventions offered in RCTs. This has also been reported in past literature. Parental reasons for strongly held treatment preferences included concerns about side effects and attitudes towards new 'experimental' or 'placebo' interventions, these issues have also been reported in the wider literature. [92-95] Although altruism was often cited as a reason for RCT participation, some papers reported poor parental understanding of the process of randomisation, and perceived 'personal' benefit for their child. [105, 622]

Findings from the systematic review suggest that young people from the age of 11 upwards were willing to voice their views when given the opportunity. However, few papers in this systematic review reported the preferences of young people participating, parents' preferences were reported more frequently. Only nine papers explicitly reported the treatment preferences of young people, as well as their parents. [66, 96, 524-526, 586, 597, 601, 602] In those papers that did report young person preference, their views differed from parental views on three occasions. [66, 96, 525] In paediatric trials, parents and young people are often both involved in receiving information about the trial and making a decision about whether to take part, with support from a recruiting health professional. [383, 623] My findings are not consistent with guidance which suggests that children and young people's voices need to be more widely heard, [44, 624] or approaches to communication which aim to promote relational autonomy instead of isolated 'independence' of choice in

decision-making. [379, 625] My findings highlight the importance of planning and considering the impact that differing treatment preferences may have when discussing trial processes, specifically rationale for randomisation, equipoise and informed consent/assent. [246] Trialists should consider ways in which they might obtain young people's views on treatment preference.

Practice implications

Findings from the meta-ethnography demonstrate the way in which preference for treatment could potentially be raised by parents, or explored by recruiters at many different points in the recruitment consultation, both while understanding trials processes (the nature of the RCT, randomisation and equipoise) and in the context of understanding the treatment options open to their child (benefits, risks, access to treatment, and ongoing management of the condition). This has important implications for practice and further research investigating preference for treatment in the context of RCT discussions. It reinforces the dynamic nature of preference discussions, and the fact that preferences for treatment are not static, they may change during the course of discussions.

Findings from the meta-ethnography also demonstrate the emotional response to discussions of randomisation and treatment preference, highlighting that care should be taken to ensure parents, young people and recruiters are adequately supported at all points in the recruitment process. Parents may need to have open conversations with recruiters, about how they reconcile 'doing the best for their child' in the context

of an RCT, and how this fits with young peoples' understanding and expectations of RCT participation; as a means of 'getting better' and 'helping others'.

This in turn highlights the dynamic and important role the recruiter plays in relaying understandable and accurate information about the RCT and treatments offered, in collaboration with parents and young people. Providing balancing information about treatment options from a position of equipoise and exploring preferences may contribute to a better understanding of the trial as a whole for families but may be challenging for health professionals if they are not in a place of personal equipoise.

Although this systematic review was not seeking to report health professional preferences for treatment in paediatric RCTs, six papers did report that members of the recruiting/treating teams had preferences. [96, 381, 524, 603, 610, 616] Health professional's preferences for treatment has been reported as a factor that should be considered when investigating treatment preference in adult and paediatric RCTs. [188, 292] It has also been shown to influence recruitment to adult trials. [90, 177, 179, 626] In one paediatric trial 63% of parents said that doctors recruiting them had influenced their decision to participate. [94] Health professionals conducting and recruiting to paediatric RCTs are also weighing up the competing goals of doing the best for their patients, and striving to work towards the RCTs goals of optimising recruitment and ensuring families are able to provide informed consent. More research should be carried out to investigate the overall equipoise of local and national recruiting clinical teams, and the influence of recruiting professionals'

preferences for treatment on the decision-making processes of families considering paediatric trial participation.

Implications for future systematic reviews in this area

The search strategy used in this systematic review identified a large number of papers, (16,936) many of which were screened as not relevant (16,360). The title/abstract screen, full text review and data extraction phases took a considerable amount of time and resource, (nine individuals over the course of two years). The search strategy included the term 'satisfaction' (Appendix 2: MEDLINE Search Strategy), this was unhelpful because it returned a high number of irrelevant papers reporting patient or parent satisfaction with treatment outcomes, not preference between treatment groups (n=272). These papers were not excluded until the full text review stage. To reduce the amount of time and resources required to complete a similar review in future, authors may choose to specifically focus on a specific condition or area of interest (e.g. CFS/ME, diabetes, surgical, or neonatal RCTs).

The current review lacked clusters of search terms to retrieve 'qualitative' papers. However, the way in which qualitative papers are indexed has been described as *'less accurate than the indexing of quantitative studies'*. [627] [pg. 223] The ORRCA project (Online resource for Recruitment Research in Clinical triAls) has developed a database of categorised research papers investigating recruitment related issues in RCTs (see: Chapter 1, Section 1.7: Treatment preference and randomised controlled trial research). The ORRCA team also identified a lack of indexed studies addressing recruitment issues in paediatric populations (those under the age of 18-years). [293,

628] Since the current systematic review was conducted, two authors have developed PUBMED search strategies, specifically designed to identify papers reporting ‘patient preference’. [629, 630] Patient preference search strategies could be tested and adapted with paediatric and RCT search terms, to develop a more focused search strategy. Therefore, a future systematic review of literature in this area should include an initial review of papers indexed via the ORRCA database, and scoping reviews using a combination of: qualitative, paediatric, patient preference, RCT and (possibly) ‘condition’ search term clusters.

4.5 Chapter summary

This systematic review has demonstrated that treatment preference can be a barrier to recruitment to paediatric RCTs. In some cases, this can result in the need to change the design of the trial (introduction of preference groups), extend recruitment or can result in trial closure. Further investigation is needed to understand the impact treatment preference has on retention, and the outcomes under investigation in paediatric trials. Only two papers included qualitative data relating to young people’s preference for treatment, synthesised data from these papers were expressed as the line of argument: **‘**Wanting to get better and help others’. Parents’ understanding of trial processes (e.g., randomisation and equipoise) and motivations for consent to their child’s participation (perceptions of the benefits and risks associated with treatment groups, access to treatment, and long-term management of their child’s condition) were factors that promoted discussion of preference for treatment. Some parents were emotional when provided with information of their child’s allocated treatment group, or when recalling aspects of the recruitment consultation. This emotional response seemed to relate in part to their preferences for a specific trial

group, not their more general views about being offered an opportunity for their child to participate, which in many cases were more positive. Synthesised data relating to parent preferences were expressed as the line of argument: ‘Doing the best for my child’. Findings from the meta-ethnography demonstrate that preferences for treatment can be raised by parents, or explored by recruiters at many different points in the recruitment consultation which has important practical implications for training health professionals who recruit to paediatric RCTs. The views of health professionals recruiting to trials were also identified as important in terms of guiding and influencing parents at all stages of the recruitment process, particularly in relation to preference for treatment, (this will be discussed in more detail in Chapter 6, Section 6.2.5: Equipoise, uncertainty and competing moral demands). This systematic review acts as a starting point for further exploration of treatment preference.

Chapter 5: **Findings: Qualitative methods embedded in four paediatric randomised controlled trials**

5.1 Overview of chapter

This chapter explores expressions of preference in four RCTs, (SMILE, MAGENTA, FITNET-NHS and CONTRACT). A breakdown of each data sample by data type (e.g. audio-recordings and interviews) can be found in Section 5.2. Exploration of how and when preferences were expressed, reasons for preference, and the way in which recruiters responded to preference are reported thematically in Section 5.3. I delivered training to recruiters that focused on communicating equipoise and exploring preferences for treatment. Qualitative examples of the way in which training influenced and changed communication practices in each RCT are discussed at the end of Section 5.3.2 'Equipoise, language and misperceptions about treatment', and in Section 5.3.3 'Understanding how recruiters' respond to treatment preference' (see text boxes). Data relating to preference for treatment and its impact on participant flow, recruitment, and retention are reported in Section 5.4, along with the impact that training had on recruitment figures.

5.2 Data samples

5.2.1 Audio-recorded recruitment consultations

Recruitment consultations were routinely recorded in each of the four trials, to understand the way in which recruiters responded to preference during recruitment consultations before randomisation to each RCT. Analysis of recruitment consultations before and after training allowed for exploration of any changes in recruitment consultations e.g. more thorough exploration of treatment preferences or changes in the language used to describe treatments after training, and whether training was associated with noticeable changes in recruitment rates. Table 5:1 provides a breakdown of recruitment consultations by trial, showing the number of consultations conducted (by family) and those subsequently recorded. The number of families who consented to and declined each RCT is also shown. Missing consultation data varied between trials with the largest number of unrecorded consultations in the CONTRACT RCT (n = 57, 50%) and the lowest number in FITNET-NHS (n = 6, 6%). Table 5:2 provides a breakdown of the number of audio-recordings analysed from each RCT, including whether analysed consultations corresponded with families who had consented to or declined the trials. Table 5:3 provides an overview of the duration of recruitment consultations recorded during the four RCTs.

Ten young people were not present when their parent conveyed their decision to decline the MAGENTA trial. In the CONTRACT trial many young people were not involved in the recruitment consultations, ten made no verbal input to the conversation and many provided very minimal input to the discussion. In contrast

young people were present during every recruitment consultation recorded from SMILE and FITNET-NHS, their level of involvement in the conversations about the trial varied depending on current CFS/ME symptoms and age, but all made some contribution to recruitment conversations and either assented or consented to the trials. Table 5:4 provides details of baseline data for all trial participants (participant age, onset of illness and school attendance).

Table 5:1 The number of recruitment consultations recorded in each RCT

Trial	Declined prior to recruitment consultation	**Family participated in recruitment consultation**	Consented to RCT	Declined RCT	Family uncontactable	**Recruitment consultations recorded and accessible**	Recruitment consultations not recorded (%)
SMILE	49	**133**	100	33	3	**90**	43 (32%)
MAGENTA	23	**130**	80	50	8	**107**	23 (18%)
FITNET-NHS	35	**96**	83	13	0	**90**	6 (6%)
CONTRACT	n/a	**115**	57	58	n/a	**58**	57* (50%)

**Fifty-eight recruitment consultations were available for analysis (20 with families who did not consent to the RCT, and 38 with families who did go on to consent). A further 19 families provided consent to the trial, and 38 families were approached but did not provide consent (see: CONTRACT CONSORT diagram Appendix 7).*

Table 5:2 The number of Recruitment consultations analysed from each RCT

Trial	Recruitment consultation data analysed (% of consultations conducted)	Consented to RCT analysed	Declined RCT analysed
SMILE	90 (68%)	89	1
MAGENTA	88 (68%)	58	30
FITNET	70 (73%)	66	4
CONTRACT	58 (50%)	38	20
Totals	**306**	**251**	**55**

Table 5:3 Descriptive data: Recruitment consultations

Trial	Number of sites	Number of recruiters	Recruitment consultation duration (range minutes)	Recruitment consultation duration (average minutes)
SMILE	1	3	7- 87	45
MAGENTA	2	4	2- 54	30
FITNET	1	4	15- 91	50
CONTRACT	3	25	0.38 – 24 minutes	9

Table 5:4 Baseline participant data: Participant age, onset of illness and school attendance by trial

Trial	Age (median) (25 percentile, 75 percentile)	N	Onset of illness (baseline) CFS/ME RCTs (Months) Acute appendicitis (24hr clock, to the nearest hour)	N	School attendance days (baseline)	N
SMILE	15 (14, 16)	98	12 (8, 20)	98	3.0 (0.5, 4.0)	99
MAGENTA	14 (13, 16)	80	15 (10, 30)	79	3.0 (1.0, 4.0)	77
FITNET-NHS	15 (13, 16)	83	Not collected	83	2.0 (0.5, 4.0)	83
CONTRACT	10 (8, 11)	57	13 (11, 19)	39*	n/a	n/a

** Onset of abdominal pain unknown for n = 17 participants and one family withdrew consent to use data.*

5.2.2 Interviews with young people and their parents

Young people eligible for each trial were also eligible to take part in an interview and families were purposively selected to participate in interviews during all four paediatric trials (See: Section 3.4.6: Sampling and sample size for interviews). Ninety-three families participated in interviews, and the Contribution Statement shows a breakdown of the number of interviews I conducted, and the number conducted by other researchers working on each trial. Collectively I interviewed half of the families who participated in qualitative interviews across three of the four trials (n= 50, 54%). Table 5:5 provides an overview of the interviews conducted in each trial. Tables showing interview participants' age, gender, socio-economic status, status in trial (recruited, declined, discontinued treatment) treatment group by trial and site ID are located in Appendix 9.

Five mothers were interviewed at all three time points during the SMILE RCT, with all remaining parents in the MAGENTA, FITNET-NHS and CONTRACT trials taking part in one-off interviews. All young people were interviewed at one time point across the four trials. Parent interviews lasted from 20 to 90 minutes and patient interviews were between 15 and 60 minutes. Eighty-three interviews were matched with corresponding recruitment consultation data.

Views of families have been prefixed with a trial ID: 'C' CONTRACT (including the corresponding site D, E and F), 'F' FITNET-NHS or 'M' MAGENTA and a participant number (e.g. SMILE: Young Person S70, CONTRACT: Young Person CF20) to denote the trial from which the data were collected.

Table 5:5 The number of families approached and interviewed in each RCT

RCT	Number of family members approached	Number of interviews: Parents (% mother)	Number of interviews: Young people (% female)	Number of families participating in interviews
SMILE	15 Young people 13 Mothers	13 (100% Mother)	12 (75% Female)	13
MAGENTA	41 Young people 40 Parents	30 (94% Mother)	27 (63% Female)	32
FITNET-NHS	28 Young people 32 Parents	22 (86% Mother)	18 (67% Female)	20
CONTRACT	28 Young people 41 Parents	34 (62% Mother)	14 (14% Female)	28
Totals		**99**	**71**	**93**

Fathers' participation in qualitative interviews increased over time in each trial because fathers were purposively sampled. Due to the high prevalence of CFS/ME in young female adolescents, more female patients were interviewed than males in the three CFS/ME trials. Conversely, more male participants were interviewed during the surgical trial because of the higher prevalence of appendicitis in adolescent males. Fourteen families (15%) had either discontinued their allocated intervention or

crossed from one intervention group to the other when they were interviewed. Fourteen families (15%) were interviewed because they declined a trial (see: Table 5:6). Twenty-two young people (31%), were interviewed without their parent present (see: Table 5:7).

Table 5:6 Families interviewed: consented or declined participation

Trial	Total Interviews	Families who consented	Families who declined
SMILE	13	13	0
MAGENTA	32	27	5
FITNET-NHS	20	20	0
CONTRACT	28	19	9
Totals	**93**	**79**	**14**

Table 5:7 The number of young people interviewed with their parent present

Trial	Total Interviews	Individual	Joint	Parent present during conversation
SMILE	12	6	6	0
MAGENTA	27	9	12	6
FITNET-NHS	18	4	14	0
CONTRACT	14	3	11	0
Totals	**71**	**22**	**43**	**6**

5.2.3 Interviews with clinical teams

Interviews were conducted with members of the two clinical teams involved in recruitment and delivering treatment during three of the paediatric RCTs: MAGENTA, FITNET-NHS & CONTRACT. Health professionals either worked in the field of specialist paediatric CFS/ME or paediatric surgery. Health professionals were purposively selected for interview and 58 participated in interviews. The Contribution Statement shows a breakdown of the number of health professional interviews I conducted, and the number conducted by other researchers working on each trial.

Table 5:8 provides an overview of the interviews carried out with members of the clinical teams. The remaining health professionals did not respond to email requests or stated they were too busy to participate.

Table 5:8 Health Professional interviews

RCT	CFS/ME Specialists	Surgeons	Research nurses and nursing staff
MAGENTA	12	n/a	0
FITNET-NHS	8	n/a	2
CONTRACT	n/a	25	10
Total	**20**	**25**	**12**

During the MAGENTA RCT the majority of the CFS/ME specialists interviewed (n = 11) were responsible for consenting families to further contact from the research team and delivering follow-up AM or GET interventions to participants recruited to the trial. One member of the team was responsible for conducting recruitment consultations in addition to delivering treatment to those participating. Interviews were carried out with nine health professionals who delivered specialist CFS/ME treatment in the FITNET-NHS internal pilot. Three of these health professionals were also responsible for conducting recruitment consultations. One interviewee was a research nurse who recruited to several different paediatric research studies across the hospital site.

Thirty-five members of three paediatric surgical teams were interviewed during the CONTRACT RCT (Site D: n = 11, Site E: n = 15 and Site F: n = 9). Twenty-five surgeons were interviewed, 15 of whom had recruited to the trial and 10 who had not

actively recruited at the time of their interview. Seven research nurses who were supporting recruitment and three ward nurses were interviewed. Five members of the three teams were interviewed on two occasions (Site D: n = 1, Site E: n = 1 and Site F: n = 3) this included two research nurses and three surgeons. Eleven of the surgeons who were interviewed also conducted recruitment consultations which were recorded and had corresponding family interview data (Site D: n = 4, Site E: n = 4 and Site F: n = 3).

Views of recruiters have been prefixed with a trial ID: ‘C’ CONTRACT, ‘F’ FITNET-NHS or ‘M’ MAGENTA and a recruiter number (e.g. MAGENTA: Recruiter M1) to denote the trial from which the data were collected. CONTRACT Recruiters IDs also include the corresponding site ID (Site D, E and F). Views of health professionals (who were not recruiting participants but were delivering RCT treatments) have also been prefixed with the trial ID: ‘C’ CONTRACT, ‘F’ FITNET-NHS or ‘M’ MAGENTA (e.g. FITNET-NHS, Health professional A: ‘FA’) to denote the trial from which the data were collected. Some health professionals referred to the MAGENTA trial during interviews about the FITNET-NHS trial, because FITNET-NHS interviews were conducted while the MAGENTA trial was still recruiting.

5.3 Expressions of treatment preference in four paediatric trials

5.3.1 How and when preferences are expressed

Content analysis (see: Section 3.5.2) was used to determine the frequency and strength of expressed preferences during SMILE recruitment consultations. During the SMILE RCT most young people did not give any indication of treatment preference, see Figure 5:1.

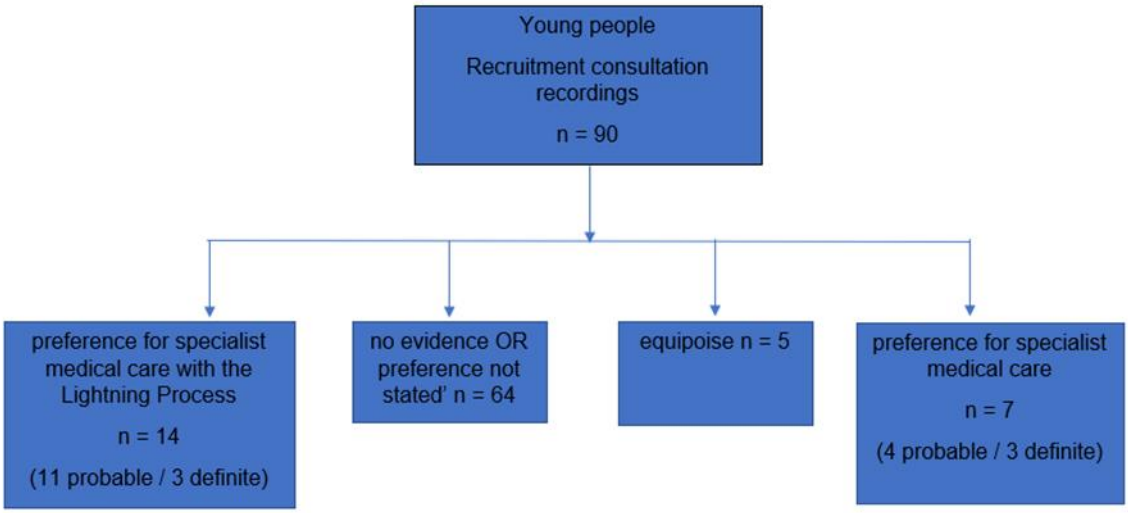


Figure 5:1 SMILE: Number of young people expressing a preference for treatment

Sixty-four consultations (71%) were coded as 'no evidence/preference not stated'. Although young people were asked direct questions about how they felt about joining the RCT, and whether they preferred one treatment in the trial over the other, in many cases young people appeared uncertain about how they felt. Fourteen were coded as preferring specialist medical care with the Lightning Process, and eleven of

these were coded as ‘probable’. Young people who expressed a probable preference didn't follow this up with reasons for their preference. This was usually because the recruiter did not try to elicit this information from the young person, or the young person’s parent interjected in the conversation. Three young people were coded as having a ‘definite’ preference for specialist medical care with the Lightning Process, they repeated their preference at various points throughout the consultation and/or they gave definite reasons for preferring this treatment. Seven were coded as preferring the specialist medical care group, (four probable and three definite). Five were coded as being in ‘equipoise’ prior to randomisation.

Preference unclear

Recruiter S4: Yeah… how would you feel if you were allocated either [treatment]?

Young person S85: I don’t mind either way

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 17yrs Male

***Definite preference* for Specialist Medical Care plus Lightning Process**

Young person S25: My only concern with it would be, in however many months if I’m still feeling awful and wasn’t in the group that had the Lightning Process, and wanted to try that as another option of something to try, would I then just pull out of the study?...My only worry is, it [Lightning Process] is the thing that makes me feel better, I don’t want to sign myself off from not doing it for a year

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 17yrs Female

Probable preference for Specialist Medical Care plus Lightning Process

Young person S96: it's worth a shot, yeah, I mean I've heard, one of my friends said she knows someone who had tried it [Lightning Process] and it worked for them, so yeah, I mean it would be a bit annoying, obviously if you didn't, but I'm not like strongly opposed to one or the other

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 16yrs Female

***Definite preference* for specialist medical care**

Young person S31: no there's nothing really, I just don't wanna be sat round a table talking for half a day…it's just I don't want to do it [Lightning Process].

Recruitment consultation:SMILE Specialist Medical Care 12yrs Female

Probable preference for specialist medical care

Young person S99: Yeah, I think I can do the questionnaires…

Mum S99: Its whether you want to do that [Lightning Process] course? I can tell from your…

[young person laughs]

Recruiter S2: would you like me to go away, so you can have a little think?

Young person S99: Yeah.

Recruitment consultation:SMILE Specialist Medical Care 14yrs Female

Equipoise

> *Young person S23: I can't really lose cos I'll be getting the treatment I would have got anyway, even if I'm not in the Lightning group, and it'll help people after, it's more if it doesn't help me then it will help people understand different things…*
>
> *Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 15yrs Female*

At times it was unclear whether young people were in equipoise, indifferent, or simply agreeing to trial participation to please their parent (or potentially the recruiter). If recruiters paused and ceded the floor when discussing the study with young people, parents often cut in and either changed the course of the conversation or expressed their feelings about treatment or their child's participation in the RCT (see: Complexity of triadic consultations):

> *Recruiter S2: what do you think up til now, how do you feel about it [the study]?*
>
> *Young Person S42: umm, yeah, I'm not sure really, yeah, I'd like to probably discuss it, a bit more before I make any, like, firm decision, but, yeah, it seems like a good thing, yeah, worth trying, just to see…*
>
> *Recruiter S2: as far as being involved with the study is concerned, the only things we're doing is asking you to fill in these questionnaires for us [continues to explain questionnaire]*
>
> *Mum S42: If we ended up on the 50% that wasn't on the Lightning project would we just continue as we are, or would we have to start again?*
>
> *Recruitment consultation:SMILE Specialist Medical Care 18yrs Male*

Young Person S65:…and that's clarified the rest of it. I don't see any problem with it personally I ...

Mum S65:…Neither do I but I wouldn't have to be doing it so you know the thing is, I mean there's nothing unusual about it, they're all, I mean it sounded like the cognitive behaviour bit of it, I know it's not, but the equivalent of….

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 15yrs Female

In contrast a larger number of parents expressed treatment preferences for trial interventions, see Figure 5:2.

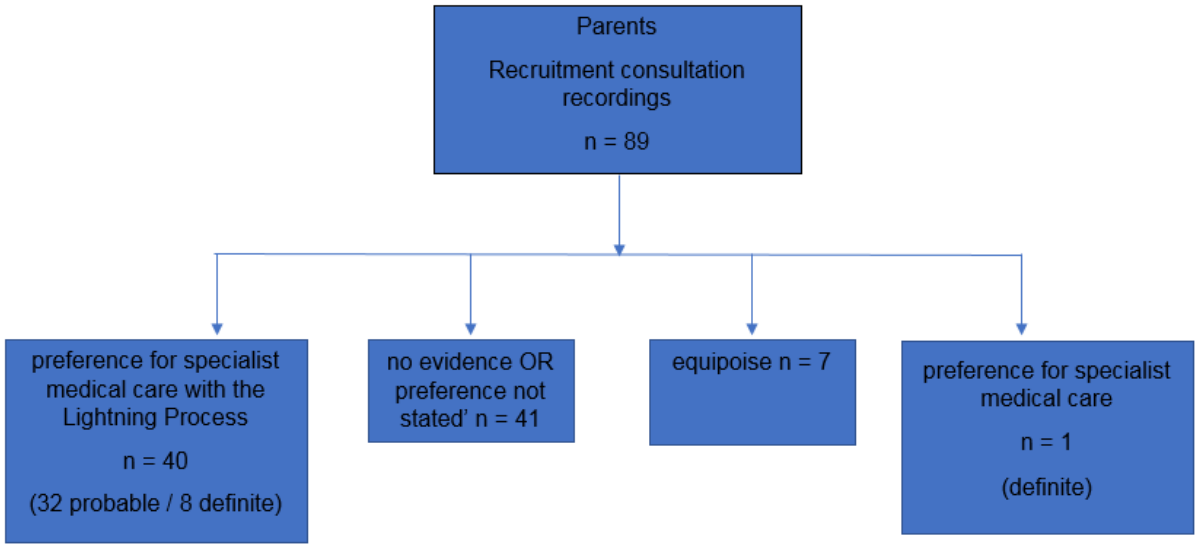


Figure 5:2 SMILE: Number of parents expressing a preference for treatment

Forty parents (45%) were coded as preferring specialist medical care with the Lightning Process (32 probable, eight definite preference) and one had a 'definite' preference for the specialist medical care group. Forty-one did not express treatment preferences. Seven were coded as being in 'equipoise' prior to randomisation, none

of these were parents of the young people who expressed equipoise. One young person discussed the trial without their parents present. Three parent/child pairs expressed conflicting preferences, (see: Conflicting parent-child preference).

Preference unclear

> *Mum S101: I've only heard about it [Lightning Process] through a friend, who knew somebody that had done this, and… raved about the results.*
>
> *Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 16yrs Female*

Definite preference for specialist medical care and the Lightning Process

> *Mum S52: I think we're quite keen to do it, [Lightning Process course] I think it would benefit [patient name] to get to talk to other people in her age group that have the symptoms, I don't know, she must feel quite isolated, and we do as parents almost as well because, I can't experience what she's going through.*
>
> *Recruitment consultation:SMILE Specialist Medical Care 16yrs Female*

> *Mum S84: We're very much of the mind, I mean we don't like, you don't like taking tablets, if body and mind can work together and it's as natural as possible I think that's more beneficial for the individual, mentally, physically, emotionally from all aspects really, so for us it's [Lightning Process course] a really positive, it's a holistic thing, it encapsulates everything.*
>
> *Recruitment consultation:SMILE Specialist Medical Care 16yrs Female*

Probable preference for specialist medical care and the Lightning Process

Mum S37: We've done some clinical hypnotherapy… we quite like the hypnotherapy but it didn't work out time wise… cos it [Lightning Process] might help might it, there's no guarantee is there, but it might help. Or [?you?] might get better just as we're going now, doing our gradual increase, [specialist medical care] might be the same….

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 12yrs Female

Definite preference for specialist medical care

Mum S70: Because I don't agree with it [Lightning Process] and you're not 18 and I wouldn't agree to you being hypnotised.

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process17yrs Female

[After establishing that hypnotism was not part of the Lightning Process course, parent accepted randomisation for their child.]

Probable preference for specialist medical care

n/a

Equipoise

Mum S13:…we're happy whichever group we end up in, because, you know if we're in the control group then we'll feel we'll be helping the study without actually having to put ourselves out, other than to fill in a few questionnaires, umm, and if we end up in the group that has the Lightning Process then that's going to be interesting and possibly very helpful.

Recruitment consultation:SMILE Specialist Medical Care 13yrs Female

Parents were more likely to express 'probable' preferences before randomisation during the course of the recruitment consultation, expressing more 'definite'

preferences after the recruiter told them their intervention allocation (see: Elation or relief post allocation). Young people generally expressed preferences for one of the trial interventions after their intervention allocation had been given to them.

The themes presented below relate to families' reactions to randomisation across all four RCTs. During the SMILE, MAGENTA and FITNET-NHS trial consultations, families' responses to their random allocation were audio-recorded as part of the recruitment consultation. Recordings of families' responses to randomisation were not routinely made during the CONTRACT RCT, therefore, only interview data were available in relation to families' responses to randomisation. Participants and parents often discussed preferences for treatment when making decisions about stopping treatment or trial participation. Table 5.9 provides details of the thematic framework used to organise themes across the four RCTs.

Table 5:9 Thematic framework. Expressions of treatment preference in four paediatric RCTs

Expressions of treatment preference in four paediatric trials	SMILE	MAGENTA	FITNET-NHS	CONTRACT
How and when preferences are expressed				
Elation or relief post allocation	✓	✓	✓	✓
Disappointment post allocation	✓	✓	✓	✓
Conflicting parent-child preference	✓	✓	✓	✓
Conflicting parent-parent preference				✓
Complexity of triadic consultations	✓	✓	✓	✓
Young people struggled to recall information	✓	✓	✓	✓
Missing conversations from the consultation process	✓	✓	✓	✓
Absent family members, decision making and preference for treatment				✓
Preference discussions can happen at any time during the consultation	✓	✓	✓	✓
Reasons for preferences				
Recovery: Wanting help to get better	✓	✓	✓	
Recovery: Wanting to get better as quickly as possible				✓
Recovery: Practicalities and family circumstances				✓
Access to treatment: A new angle, something different	✓	✓	✓	✓
Access to treatment: Affordability	✓			
Access to treatment: Positive results or recommendations	✓		✓	
Being better suited to a specific treatment	✓	✓	✓	✓
Active (positive) versus Control treatment	✓		✓	
Experimental versus Standard (positive) treatment		✓		✓
Risk of harm	✓	✓	✓	✓
More is better ‘pick and mix’ approach’	✓	✓	✓	
Past experience of intervention		✓		✓
Anxieties about treatment and treatment delivery	✓	✓	✓	✓
Misunderstandings: Evidence-based treatment		✓	✓	
Misunderstandings: Therapeutic misconception				✓
Altruism	✓	✓	✓	✓
Equipoise, language and misperceptions about treatment	✓	✓	✓	✓

Table 5:9 continued

Thematic framework: Expressions of treatment preference in four paediatric RCTs

Expressions of treatment preference in four paediatric trials	SMILE	MAGENTA	FITNET-NHS	CONTRACT
Understanding how recruiters' respond to treatment preferences in paediatric trials				
Acceptance of preference and missed opportunities to explore preference	✓	✓	✓	✓
Exploring preference	✓	✓	✓	✓
Health professional and recruiter equipoise				
Individual versus collective equipoise	n/a	✓	✓	✓
Discussing uncertainty and equipoise: what would you do?	n/a	✓	✓	✓
Questioning the eligibility criteria	n/a	✓	✓	✓
Discontinued treatment, treatment failure and recurrence	n/a	✓		✓
The impact of treatment preference on recruitment and retention in four paediatric RCTs				
Consent to trial despite preference for treatment	✓	✓	✓	✓

Elation or relief post allocation

Parents in the three CFS/ME trials who received their preferred treatment were often elated when they were given their child's random allocation:

> *Parent S8:…you're having the lightning treatment, oh that's brilliant*
>
> *Young Person S8: Oh, I'm pleased with that.*
>
> *Parent S8: [laughs]…oh [patient name] I am pleased!... I'm feeling all emotional a minute, oh it's fantastic [mum tearful].*
>
> *Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 16yrs Female*

Young peoples' responses to randomisation in the three CFS/ME trials were more reserved. One young person suggested her approach to trial participation was *"cautious"*, she had not expressed her preference for CBT treatment (this was brought up by her dad during interview), because her past experience of treatment for CFS/ME had been disappointing and she didn't want to get her hopes up:

> *Young person F12:…When we went through [discussed] both sides I said I didn't mind which one I would be put into…*
>
> *Dad F12:… honestly I think [patient name] was a little bit reserved at that point, [before randomisation]…obviously her hope was that she'd go onto the CBT side of the study, but there was no expectation at that point…*
>
> *Young person F12:…Yep. I was definitely cautious. I didn't want to get my hopes up because of being let down and disappointed by my experience at [other hospital].*
>
> *Interview:FITNET-NHS Online CBT 16yrs Female*

Disappointment post allocation

Parents in each of the four trials reported disappointment when their child was randomised to their non-preferred treatment group. Some families reported disappointment but continued with their allocated intervention. This was most apparent during the SMILE trial. Parents were often more openly disappointed than young people immediately after being informed of their child's allocation of Specialist Medical Care:

> *Young Person S42:…I don't mind, I'm happy to try it yeah, nothing else has worked, [mum and young person laugh] I think it would be worth giving it a go.*
>
> *Recruiter S2:…you've been allocated to the Specialist Medical Care group.*
>
> *Young Person S42:…Yep, good.*
>
> *Parent S42:…I'm a bit disappointed.*
>
> *Recruitment consultation:SMILE Specialist Medical Care 18yrs Female*

Health professionals recruiting to CONTRACT reported that families expressed disappointment when they were not allocated to their 'preferred' treatment group (antibiotics). One CONTRACT mum described disappointment when her child was not allocated to her preferred treatment and also described the manner in which she was informed of the allocation as insensitive:

> *Mum CD19:…I was talking to a nurse… the consultant came 'round and said 'no, sorry, she's not got it', I was like, 'what? Not got what? What?' So that was a bit of a blow. I think I'd rather have been told away from her*

about that… that felt like it was thrown at me... that seemed to happen quite quickly.

Interview:CONTRACT Appendectomy 6yrs Female

Although parents often reported disappointment after allocation to their non-preferred treatment group, sometimes after experiencing their non-preferred treatment, the preference dissipated:

Mum F20:…so when I thought, "Ooh, we can do it online," I thought, "Yes, that would be great. We'll see if that could benefit her." So, I was disappointed when we got the activity management, but you know, fine, we'll go for it, and actually, I'm so glad, because I think it's been quite important, what we've learnt with this. Without the activity management advice, I don't know if any CBT would have helped her, because she'd still be doing all that high-energy activity, so it's worked out beautifully. I'm really pleased.

Interview:FITNET-NHS Skype activity management 13yrs Female

Conflicting parent-child preference

Some young people in all four trials had a different preference from their parents. In most cases, when conflicting preferences for treatment were apparent, they were discussed between families and recruiters. Families opted for trial participation when parents felt their child was keen to participate, and if parents felt sufficiently reassured about their non-preferred treatment to consent to their child's participation:

Young Person S70:…Can't I do it [trial]

Mum S70: No.

Young Person S70: Why?

Mum S70: Because I don't agree with it and you're not 18 and I wouldn't agree to you being hypnotised.

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 17yrs Female

[After establishing that hypnotism was not part of the Lightning Process course, parent accepted randomisation for their child.]

Young Person F18:…I was just excited to know that I was going to do one of them.

Mum F18:…I think I was a bit different. I was really keen that [participant] did the FITNET side of the study, partly because we'd been trying to manage with activity anyway, and it was just, sort of doing less and less and less …

Interview:FITNET-NHS Online CBT 13yrs Male

Mum CD18:…[Patient] broke down [when he heard which treatment he was allocated]… and I had a secret high five… he was really adamant he wanted the antibiotics and I think he was really gutted that it came up he needed surgery.

Interview:CONTRACT Appendicectomy 9yrs Male

Some parents felt that their child might not 'engage' with one of the trial treatments, but because they were keen for them to enter the trial they 'encouraged' their child to participate:

Mum S34:…Yeah see, I mean he's very erm (..) analytical and very erm, scientifically minded …and he's not really into alternative therapies at all. So that's why I didn't initially tell him about it …was only after we'd been to the clinic I wasn't going to [tell him] until I knew he'd be receptive…he was a reluctant candidate even though I was thrilled that he'd been selected…

Interview:SMILE Specialist Medical Care plus Lightning Process 15yrs Male

Young Person S34:… I've always sort of turned my nose up at all of the sort of homeopathy and all of these kinds of … so I mean I've got to be honest, especially after the first day, I was really not happy about coming back… it was just completely out of my comfort zone in terms of what I think… also what I'd have thought worked.

Interview:SMILE Specialist Medical Care plus Lightning Process 15yrs Male

[Mum and young person interviewed separately.]

At other times a parent and child did not have a conflicting preference, but they did have a conflicting opinion about whether they should join the trial. Only one instance of this occurred during the MAGENTA RCT, and it was the young person who made the final decision about trial participation. This participant's parents would have declined the trial, but since their daughter was 17 years old, she decided she wanted to take part, but crossed-over to her preferred treatment at the six-month point:

Young person M35:…Just because I'd already tried this side [activity management] and it hadn't worked before, so I was sort of wondering if maybe like the other side would work. But, I'm happy to try this side and see if it works better, now I'm older kind of thing.

Interview:MAGENTA activity management 17yrs Female

[Discontinued treatment at 6 months to do Graded Exercise Therapy.]

Mum M35:…we would have joined without hesitation if we were getting the new treatment, [Graded Exercise Therapy] different one from what we tried before. [participant's name] took the decision herself, said she was going to go for it, and then of course, she got the wrong one…

Interview: MAGENTA activity management 17yrs Female

[Discontinued treatment at 6 months to do Graded Exercise Therapy.]

Similarly, the preferences of young people were at times unclear (see also Complexity of triadic consultations), especially when families were interviewed retrospectively about the preferences they had when they were considering trial participation. The participant below *"agreed"* with her mum's preference for FITNET online CBT during the recruitment consultation, *"have you got any thoughts about either of the two sides of it [treatments]"*:

Mum F23:…I think the cognitive behaviour [FITNET-NHS Online CBT] one would be better for her. I think with the activity management one, I think it's similar to some of the things that were suggested by the chronic fatigue service. I think she's got to get to a stage where she can accept her condition before she moves on. She's got all the information about the activity management and about pacing herself, she is still refusing to do that.

Young person F23:…Yeah I agree with that, I don't know like, it is hard for me to like accept my condition, that sort of side will be more useful for me I think.

Recruitment consultation:FITNET-NHS Online CBT 16yrs Female

However, retrospectively at interview this young person discussed her preference for a *"face-to-face"* mode of treatment where *"you've got a physical person",* also highlighting that preferences for treatment during the FITNET-NHS trial could be based on mode of treatment (face-to-face skype versus Online email) and/or content of the treatment pathway (Activity Management or CBT):

> *Young person F23:…The FITNET, she did explain it was a lot of content to cover. So she did warn me about that and then she said the other one, it was something about Skype calls, more face-to-face thing.*
>
> *Mum F23:…I think, had you have been able to choose, you would have chosen the other one.*
>
> *Young person F23:…Yeah. Face-to-face… for me it would be more effective …you've got a physical person who's telling you specific coping strategies to do and I think it's more effective than completing tasks.*
>
> *Interview:FITNET-NHS Online CBT 16yrs Female*

Conflicting parent-parent preference

At times during CONTRACT recruitment consultations it became apparent that parents had different preferences, although it was not always apparent how these differences were resolved. In many cases it seemed the resolution might have occurred during unrecorded family discussions:

> *Mum CD6:…I think we should try the antibiotics, yeah.*
>
> *Dad CD6:….Are you sure?*
>
> *Mum CD6:…I am sure.*
>
> *Dad CD6:…But it might come back later on in life when he's older...which is worse.*

Mum CD6:…But she said..... a 10% chance.

Dad CD6:…Will he pull that [canula] out or...

Mum CD6:…He's been gentle with it. He'd rather have that than go and have an operation.

Recruitment consultation:CONTRACT Antibiotics 8yrs Male

One recruiter reflected upon one occasion where parents differed in relation to their preference for treatment, *"it's fair to say that kind of one parent feels one way about what they want, and another parent feels another way"* with the recruiter suggesting that randomisation offered a solution to this difference of opinion:

Recruiter CD9:…So they've decided that because, you know, we haven't got a definite plan of what we want to do, you're happy to go into the research study where the computer chooses, and then we go with that option until, you know, unless you change your mind or if, you know, as I said he has the antibiotics and then he doesn't respond.

Dad CD5:…Yeah.

Recruitment consultation:CONTRACT Appendectomy 9yrs Male

Complexity of triadic consultations

Instances where parent and young peoples' preferences for treatment differed added an element of complexity to communication and decision-making. During recruitment to CFS/ME trials often only one parent (usually the mother of the child) was present during the consultation, and it was sometimes difficult to ascertain the extent of young peoples' preferences during these conversations. During CONTRACT recruitment consultations there were more occasions when both parents were

present to discuss the trial with the recruiter. This adding a level of complexity, and multiple occasions where mothers and fathers differed in their preferences for treatment (see: Conflicting parent-parent preferences).

Young peoples' engagement in recruitment conversations varied widely, with some taking the lead during consultations, specifically when their parent left the room for any period of time. Other young people said very little unless specifically prompted by their parent or the recruiter. At times it was difficult to gauge their feelings about interventions, specifically when young people appeared to 'agree' with statements made by their parent:

> *Mum F17:…I think I would have preferred the Skype one. The activity management, just because of the contact.*
>
> *Young Person F17:…Yeah.*
>
> *Mum F17:…I feel it would have been a lot better for us. Do you [name]?*
>
> *Young Person F17:…Yeah.*
>
> *Recruitment consultation:FITNET-NHS Online CBT 15yrs Male*

Young peoples' preferences were not always expressed as strongly as parents' preferences for treatment during recruitment consultations or interviews in all four trials. During recruitment to the CFS/ME trials, young people appeared more accepting of either trial group:

> *Young Person F14:…I suppose I would like the exercise one to see, to go back into the exercise and see how I manage with it all kind of thing. I am*

open for either because I know that either would benefit me, so I am not particularly fussed to be fair.

Recruitment consultation:FITNET-NHS Online CBT 17yrs Female

Young person M109:…[what did you think about having treatments allocated by randomisation?] Erm, I don't really mind to be honest. I was happy with either one.

Interview:MAGENTA Graded Exercise Therapy 17yrs Male

There were also instances where parents interrupted or answered question on their child's behalf. On some occasion's parents appeared to want to help their child if they were struggling to find an answer:

Recruiter F1:…Right. Have you thought about the difference between the two groups?

Young Person F10:…Um, um, [pause]…

Mum F10:…I don't know whether [child] has or not. I certainly have.

Recruiter F1:…Right.

Recruitment consultation:FITNET-NHS Online CBT 16yrs Female

Some young people felt confident enough to correct their parents when they felt they were presenting their symptoms or views differently from how they perceived the situation, as demonstrated below. Although this extract is not directly related to preference it highlights the way in which young people and their parents may perceive events and situations differently:

Mum F13:…with a bit of help from the school counsellor and a bit of time it [anxiety] sort of sorted itself out didn't it… is that fair [name]

Young person F13:…I'd say it was a lot of help from the school counsellor, it didn't exactly sort itself out, it was more….

Mum F13:…What I mean then is the symptoms you were having then have, you don't get panic attacks any more do you?

Young person F13:…No I don't.

Recruiter F1:…Okay that's great.

Recruitment consultation:FITNET-NHS Skype activity management 15yrs Female

Due to age (median age 10yrs) and severity of illness, fewer young people who were eligible for CONTRACT actively participated in recruitment consultations. There was no verbal dialogue from young people during 25 consultations. It was not always clear if a young person was present but not talking, or if parents were in another room away from their child's bedside discussing the trial. Some consultations were conducted late in the evening or during the night when young people were asleep. Some parents reported that they wanted, (or would have liked) to have the recruitment consultation away from their child's bedside to reduce their child's anxieties and allow them to concentrate on the study information:

Recruiter CE10:...Now I understand that she [participant] wasn't involved in a conversation…

Mum CE20:…No, I will explain it to her. I just, I wanted to talk to you properly because she would've got upset and I wouldn't have been able to

have concentrated on what you were saying to me. So I will explain it all to her.

Recruitment consultation:CONTRACT Antibiotics 11yrs Female

Many young people participating in CFS/ME trials had spent significant time off school and had been unable to socialise with friends. Parents often reported a deterioration in their ability to engage in conversation, particularly with people they did not know. This may have been due to young people's CFS/ME symptoms, 'brain fog' (a symptom associated with confusion, difficulty concentrating and memory loss) and loss of confidence in social situations. Parents made attempts to engage their child and provide feedback to the recruiter about 'non-verbal cues', *"she's nodding" [Dad F11].* However, during analyses it was difficult to distinguish the extent to which non-engagement was due to young peoples' symptoms, negative perceptions of one or more trial interventions, or a more general lack of engagement in the research process:

Mum F11:…Okay, don't shrug your shoulders. Classic 13 years old. She's very quiet and this is the trouble. She's quiet naturally and since she's had this illness she's got even quieter. She's a little bit too passive about the whole thing.

Mum F11:…Which do you think you'd rather do?

Young Person F11:…I don't know.

Recruitment consultation:FITNET-NHS Skype activity management 13yrs Female

Young people in all four trials struggled to recall information given to them about the studies during the recruitment consultation. This was particularly apparent during interviews with young people who had participated in CONTRACT, since many of the young people had been in considerable pain, and highly anxious about being admitted to hospital:

Researcher 2:…Did they go into much detail about the two… treatments?

Young person CE7:…Yeah. Um, they did. I can't remember a lot about that actually.

Interview:CONTRACT Antibiotics 14yrs Male

[Recurrence also treated with antibiotics.]

Researcher 2:…Do you remember them telling you about the CONTRACT study?

Young person CE4:…I wasn't really listening.

Interview:CONTRACT Antibiotics 10yrs Male

[Recurrence also treated with antibiotics.]

Researcher 2:…Do you remember something on a DVD, like an iPad or a laptop? Do you remember watching something?

Young person CF9:…I remember mummy and daddy watching it… I might have done but I can't really remember.

Interview:CONTRACT Appendectomy 8yrs Female

Researcher 1:…So did she [surgeon] come in and speak to you about it? Yeah? And do you remember what she said?

Mum CD18:…So, you're on about when the doctor come in with the results, aren't you? But why, why did you want to do the study?

Young person CD18:…I don't know.

Interview:CONTRACT Appendectomy 9yrs Male

Their recollection of the two treatment groups and information leaflets was sometimes limited, particularly during interviews which occurred sometime after randomisation:

Young Person S38:…I can't remember the past four weeks, you know I can remember when I was like five, but I can't remember the past four weeks, my memory's really bad.

Interview:SMILE Specialist Medical Care 16yrs Female

Young Person M49:…I can't remember [what the other one was].

Interview:MAGENTA Graded Exercise Therapy 15yrs Male

Young person F20:…I remember getting it. [PIL] I don't remember …I did read it, yes…

Interview:FITNET-NHS Skype activity management 13yrs Female

Missing conversations from the consultation process

It became apparent that the recruitment process was split into four separate stages, only one of which was recorded, the 'main discussion', See Figure 5:3:

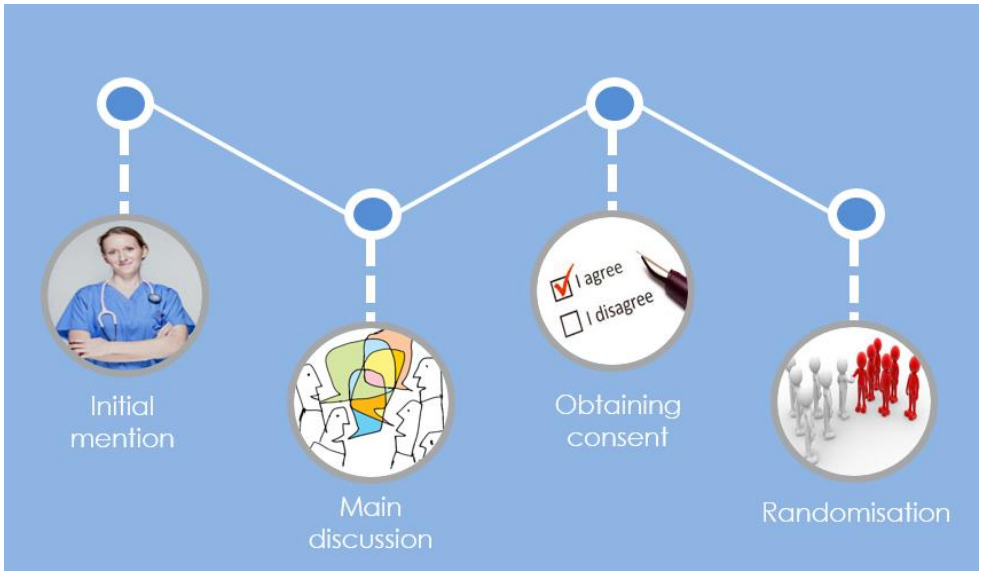


Figure 5:3 Stages of the recruitment process

1. Initial mention

All families had spoken to at least one other health professional before a recording was made of their 'main' discussion with a recruiter about the RCT:

SMILE and MAGENTA: Assessing CFS/ME specialist at the first clinical assessment appointment.

FITNET-NHS: Referring local GP or paediatrician primary care setting, and wider CFS/ME Administration team.

CONTRACT: Research nurse, recruiting surgeon or wider emergency department staff.

2-3. Main discussion, Obtaining consent and randomisation

SMILE: Member of the research team travelled to the family home and discussed the trial, gained assent/consent and used a telephone-based randomisation system.

MAGENTA and FITNET-NHS: A health professional from the specialist CFS/ME team discussed the trial with the family over the phone, gained assent/consent and used an online randomisation system.

CONTRACT: A member of the surgical team discussed the trial with the family in an acute care or observation ward setting, gained assent/consent and used an online randomisation system.

The SMILE trial highlighted the importance of recording the families' responses to randomisation. After intervention allocation many families had expressed more definite, or a first expression of preference for treatment:

> *Recruiter S4:...[name] has been allocated to the arm to receive the continuing care she would, specialist medical care… and to go on the lightning process course*
>
> *Dad S73:…Oh great [dad clapping].*
>
> *<u>Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 14yrs Female</u>*
>
> *[Participant did not attend Lightning Process course.]*
>
> *Recruiter S1:…You've been given the group for the Specialist Medical Care.*

Mum S27:…I'm really disappointed are you?

Young person S27:…?Inaudible?

Recruitment consultation:SMILE Specialist Medical Care 15yrs Female

There were instances when it was clear that an extensive conversation had already taken place between the recruiter and the family, which may (or may not) have provided information about the family's preferences for treatment. At the first phone call made by the recruiting researcher 9 families (27%) declined to hear more about the SMILE trial, because they had a preference for treatment. It was unclear how many other families had in-depth conversations with recruiters or members of the wider clinical team prior to the main recruitment consultation:

Recruiter S3:…I know we talked quite a bit on the phone, didn't we, about the study…

Mum S44:…Yes, yes, yes.

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 15yrs Female

During the MAGENTA and FITNET-NHS trials recruiting health professional's audio-recorded the main trial discussion, consent/assent process and randomisation outcome, and a high number of main recruitment consultations (82% and 94% respectively). Only 14 (13%) and 10 (14%) randomisation outcome conversations were not recorded during the MAGENTA feasibility and FITNET-NHS internal pilot. In contrast, during the CONTRACT feasibility trial, most data were obtained from audio-recordings of 'main' recruitment consultation discussions, and 50% of main

recruitment consultations were recorded and available for analyses. Multiple recruitment conversations were made with 20 CONTRACT families, (nine SMILE, 36 MAGENTA and 31 FITNET-NHS) and CONTRACT recruiters fed back via interview and training sessions that in theory it was feasible to make audio-recordings of consent and randomisation discussions. However, in practice only three 'extra' recordings were made. Whether or not it is feasible or useful to make additional records of these conversations in an acute care setting will be discussed further in Chapter 6: Discussion.

Absent family members, decision making and preference for treatment

During the CONTRACT trial it also became apparent that the recorded recruitment consultation often only involved one parent (usually the mother), who would state that she needed to contact the child's father or another family member before a decision about participation could be made. In these situations, if families declined the trial, it was difficult to understand whether preference for treatment was an issue for the absent parent:

> *Mum CE12:… Obviously it's something I'll discuss with her dad and we'll make a joint decision. But thank you for giving me the opportunity. Okay, right, I'm gonna see if I can get hold of her dad.*
>
> *Recruitment consultation:CONTRACT Declined trial 9yrs Female*

Preference discussions can happen at any time during the consultation

Preferences discussions were not specific to one 'area' of the consultation (e.g. when discussing treatment or randomisation). Preferences were particularly likely to

be discussed early in the consultation when recruiters asked families, “What do you think about the study?”. A direct question about preference, such as, “Do you have a preference for treatment?” was unnecessary and discouraged during communication training sessions. Neutral questions about treatment were encouraged “Have you got any questions to start us off about the treatments?” (Appendix 4: MAGENTA: Tips for recruitment and informed consent). Direct preference questions might incorrectly lead to families believing they ‘should’ have a preference for treatment, and result in parents or young people forming a "preference”. A lack of exploration of preference may therefore be attributable to the fact that recruiters were responding to other concepts which they felt were the main topic of discussion at that particular point in the recruitment discussion, e.g. randomisation or what the trial interventions involve.

5.3.2 Reasons for preferences

Participants and parents often discussed preferences for treatment when recruiters asked for their views on the trial, randomisation or trial treatments and these views centred around motivations or benefits (hopes) and reservations or risks (fears) about taking part in each of the three CFS/ME RCTs (see: Section 4.3.2). Some families declined because of preference for treatment whereas others were willing to consent to the trial despite having some reservations (see: Section 5.4.1).

Recovery: Wanting help to get better

Young peoples’ motivation for accessing a ‘preferred’ treatment in the three CFS/ME RCTs centred around getting better and gaining help and support with their recovery in specific areas of their illness. These areas included improving their current level of

physical fitness, better management of cognitive ‘thinking’ activities, (SMILE, MAGENTA and FITNET-NHS) or developing coping strategies to deal with unwanted or unhelpful patterns of thinking which contributed to an improvement in CFS/ME fatigue symptoms (SMILE - Lightning Process and FITNET-NHS - CBT). Some young people talked about potential for a ‘quicker’ recovery and there were perceptions that specific treatment approaches in each RCT might mean a quicker recovery. Those who had been ill for long periods of time stated they were just happy that someone was investigating CFS/ME treatments for young people; they saw participation as an opportunity to improve their current health, and return to school and social activities more quickly:

> *Young person S12:…I am really, really happy I got picked [Specialist Medical Care plus Lightning Process group] because otherwise I could have been ill for so many more years…*
>
> *Interview:SMILE Specialist Medical Care plus Lightning Process 15yrs Female*

> *Young person M20:…I prefer the sound of the physical one….my exams are really important, so if I start now, I might even be able to be, getting better for my exams…*
>
> *Recruitment consultation:MAGENTA Graded Exercise Therapy 17yrs Female*

Mum F15:…I think at the time, [patient name] would have preferred to have gone on the CBT side of the study… she said it was more a matter of well it doesn't matter that I got the other side at least it's some form of treatment and something to work with.

Young person F15:…Well obviously I would have preferred the CBT side but I, just like mum said, I don't really mind… I was just willing to give it a try really... I just wanted to get better really… It's just something really. Just a chance to get better to be honest.

Interview:FITNET-NHS Skype activity management 12yrs Female

[No recruitment consultation available.]

Recovery: Wanting to get better as quickly as possible

Young people considering recruitment to the CONTRACT RCT discussed their wish for a quick recovery. Some discussed wanting to recover for a school trip, holiday abroad or so they could start doing physical activities they had been told to stop during recovery:

Young person CE1:…I want the easier one…medication [antibiotics].

Mum CE1:…You what? You'd rather try the medication?

Young person CE1:…Yeah. 'Cause [it's] like easier, 'cause like, I've got six weeks and I'll just be indoors recovering from being cut open and that.

Recruitment consultation:CONTRACT Appendectomy 13yrs Male

Young person CE4:…I did prefer the sound of having medicine instead of the operation. Because you get to go back to things quicker…I wanted to get straight back to diving.

Interview:CONTRACT Antibiotics 10yrs Male

[Recurrence also treated with antibiotics.]

Young people with CFS/ME had typically been ill for prolonged periods of time (see: Table 5:4, Baseline participant data). If parents expressed preferences for treatment, they generally followed this with a statement that made it clear to the recruiter, they would accept either intervention:

Mum F16:…I think it would be the Skype. I think it might work better but I don't know. I think that's the way I'm leading towards, where you actually have that face-to-face contact and you can talk it through…we're desperate for anything really, so we will go with whatever is offered.

Recruitment consultation:FITNET-NHS Online CBT 16yrs Male

An urgent need for 'any' kind of treatment delivered by a specialist team to aid recovery was a more prominent theme in the FITNET-NHS RCT, because this RCT was designed for families with no access to local treatment. This was often discussed in the context of a lack of service provision in their local area. FITNET-NHS families didn't want to travel long distances to access CFS/ME services and treatment because this exacerbated symptoms:

Mum F24:…Yeah, I don't think we have anybody local to us. I know that the paediatrician was trying to find out. I think the nearest is about an hour and a half, two hours away from us.

Recruitment consultation:FITNET-NHS Online CBT 17yrs Female

Recovery: Practicalities and family circumstances

In the CONTRACT RCT, acute illness resulted in the need to make unscheduled arrangements for cover of their paid employment and/or childcare for siblings at short notice. For some families, preferences for treatment were linked to making the best decision not only for their sick child, but one that would have least impact upon the wider family given current family circumstances:

Mum CE10: …my husband's going away for a month and I'm gonna be here on my own and so if we have the antibiotics and they don't work, it's bound to fall right in the middle of that, when he's [away] and I'm here on my own…Yeah, there's a five-year-old [sibling] as well.

Interview:CONTRACT Declined trial 8yrs Male

Access to treatment

Young people and their parents discussed their reasons for a preferred treatment during recruitment consultations and interviews. Some families considering participation in the CFS/ME trials had already tried a 'form' of treatment they considered similar to, or the same as one of the study groups (predominantly activity management, (see: Past experience of intervention). In the past, use of what was identified as 'activity management' had usually been self-directed. These young

people and parents expressed a preference for accessing a ‘new’ and different treatment approach via the SMILE, MAGENTA and FITNET-NHS trials (the Lightning Process, Graded Exercise Therapy or FITNET Online CBT respectively):

> *Mum F18:…I think I was a bit different. I was really keen that [patient name] did the FITNET side of the study. Partly because we’d been trying to manage with activity anyway, and it was just, sort of doing less and less and less and I, I felt that um, a new angle on helping [patient name] recover would be helpful but yeah, having a fresh angle on the um, you know the mental strategies, as well as the physical strategies*
>
> *Interview:FITNET-NHS Online CBT 12yrs Male*

> *Young person M108:…Activity management sounded a bit like what I’d already been doing in a way and graded exercise sounded like a new thing I think because it does... it sounds like exercise; “Oh good, I’m actually going to be doing some exercise and stuff”*
>
> *Interview:MAGENTA activity management 14yrs Female*
>
> *[Withdrew from trial.]*

If young people or their parents had a preference for one of the treatments offered in the SMILE, FITNET-NHS or CONTRACT trials (because some or all treatments were not routinely accessible outside the trial), some families felt they had nothing to lose by consenting to participate:

> *Mum S9:…We were in that position that she was so unwell that actually if somebody was saying, “you can do this [Lightning Process] as part of this study”, then yes we will go for it, we’ve got nothing to lose.*

Interview:SMILE Specialist Medical Care plus Lightning Process 12yrs Female

Young person F20:…I was kind of like, "It might help; it might not help, so it's not really kind of a bad – can't really lose, so I'll just see if it helps."

Interview:FITNET-NHS Skype activity management 13yrs Female

Antibiotic treatment for acute appendicitis was not a routine treatment pathway outside the CONTRACT RCT, (see: Section 5.4.2: Retention: Preference and ongoing participation - CONTRACT):

Mum CF21:…You might decide to be in the study group because you might be really interested in an alternative option than surgery. But then, because you're randomly allocated to one branch or the other, you could be then in a situation of actually not getting what you really were quite interested in having. Do you see what I mean? Even though you decided to be in the study.

Interview:CONTRACT Declined trial 15yrs Male

Many parents could not afford to access the Lightning Process (while the trial was recruiting the course cost £620), outside the SMILE trial:

Mum S35:…Why I wanted to be involved… because I've had recommendations that there might be a programme or treatment or whatever it's called [Lightning Process]. So when I heard that there was a possibility that it might be available through this, [trial] then I thought, "Fantastic cos I haven't got the money for it"

Interview:SMILE Specialist Medical Care 12yrs Female

For some there was also a perception that the preferred treatment had already been shown to be effective in another research setting (FITNET in the Netherlands), or because of figures relating to the Lightning Process from surveys conducted with adults that were provided in the SMILE PIL (Appendix 3):

> *Young person F19:…Just the statistics of how it worked in the previous trials, in Holland was it? And just because it was something new. I think if I was on the other one, it might have been more repetition of what I've already done.*
>
> *Interview:FITNET-NHS Online CBT 14yrs Male*

> *Mum F15:…I think it was probably driven by the headlines that had come out …in terms of the success rates, the CBT side of things… and kind of jumping onto that hope really...*
>
> *Interview:FITNET-NHS Skype activity management 12yrs Female*
>
> *[No recruitment consultation available.]*

> *Mum S61:…The Lightning Process you wanna try don't you?*
>
> *Young person S61:…Yeah.*
>
> *Mum S61:…I mean the figures do look very promising, I know they are only figures on a bit of paper…*
>
> *Recruitment consultation:SMILE Specialist Medical Care 17yrs Female*

Some parents had also heard about the Lightning Process anecdotally, and knew someone else who had personally had positive results and benefited from the treatment:

> *Mum S7:…It's a long story but [name] her sister, a friend of hers, her daughter had, had ME for quite a few years and her mum had just paid for the Lightning Process and said it was fantastic, and other people had said you know, heard really good things about it.*
>
> *Interview:SMILE before randomisation. Specialist Medical Care plus Lightning Process 13yrs Male*

Being better suited to a specific treatment

Young people and parents in the CFS/ME RCTs perceived certain treatments offered in the trials as being 'better suited' to their personality, treatment needs or current lifestyle:

> *Mum S35:…It's neuro lingual programming [Lightning Process] and as far as I understand, that's… the basis of it which is a well-tested system of working, which actually I think would sadly suit [patient name] and her personality hugely well.*
>
> *Interview:SMILE Specialist Medical Care 12yrs Female*

> *Young person F21:…[discussing a preference for the activity management group] …I think it was because like I'm more of like a 'get up and go' and like kind of 'achieve' person so I was kind of aiming more towards that….*
>
> *Interview:FITNET-NHS Online CBT 11yrs Male*

In the MAGENTA RCT Graded Exercise Therapy was viewed as more appropriate if they were ‘sporty’. Activity management was perceived to be more appropriate if they didn’t like or didn’t currently do a lot of exercise. Activity management was also perceived to be better suited to those who had a heavy workload at school, and wanted advice about managing their workload, or cutting down:

> *Young person M25:…I liked the idea of the graded physiotherapy [Graded Exercise Therapy] because I play a lot of sport so getting fit…*
>
> *Interview:MAGENTA Graded Exercise Therapy 16yrs Female*

Some families with a preference for treatment declined the trials, if they knew they could access their preferred treatment, one they felt was ‘better suited’ to their child outside the trial:

> *Mum CE12:…In my circumstance my daughter really does not like taking antibiotics. She has been sick on them, she has refused, she has cried, she has stamped her feet, I can’t get her to take them. So I think in this instance, I think I’ve made my decision.*
>
> *Recruitment consultation:CONTRACT Declined trial 9yrs Female*

Families who were unsure about which treatment might suit them saw trial participation as an opportunity to take the decision about treatment out of their hands:

> *Mum F22:…I wasn't quite sure which one would be better suited for her really so, that's why I'm going to leave it in your capable hands now.*
>
> *Recruitment consultation:FITNET-NHS Skype activity management 11yrs Female*

However, several families who expressed preference for treatment still consented to the MAGENTA trial despite the fact they could access their preferred treatment outside of the trial (see: Consent to trial despite preference for treatment).

Perceptions of young people's current physical and emotional condition were considered and discussed alongside preferences for treatment during recruitment consultations and were also discussed in the decision-making process when families withdrew or discontinued interventions post-randomisation (see: Discontinued treatment, treatment failure and recurrence). Overt signs of young patient distress (such as audible crying) were more apparent during CONTRACT recruitment consultations. In these circumstances some parents opted for surgical treatment outside the trial, particularly if it was framed by recruiters as 'quicker' and more definitive. Post randomisation drop-out in the CONTRACT RCT was discussed in relation to 'treatment failure' and perceived 'deterioration' in the young person's physical state when treated with antibiotics.

Active versus Control and Experimental versus Standard treatment

Preference for the 'active' as opposed to the 'control' treatment was discussed as positive and more beneficial in the SMILE and FITNET-NHS trials. The Specialist Medical Care plus the Lightning Process group and FITNET online CBT group were referred to as 'active' trial groups by families. Recruiters had not used these terms during recruitment consultations but families either had some understanding of RCT research or this information had been passed on by a friend. However, interventions that are perceived as 'experimental' can have negative connotations in a paediatric

trial context. One father referred to FITNET Online CBT as the *"experimental one",* but this was a positive for him as it was his preferred treatment group, because he felt*: "this experiment in Holland had quite a lot of success for teenagers" [Participant F2, 13yrs, female, Online CBT group]:*

> *Mum F19:…We were obviously hoping for the active arm, but it didn't really matter because whatever you got was going to be extra, but helping him in some way that he didn't already have access to.*
>
> *Researcher F8:…And by the 'active arm', do you mean activity management?*
>
> *Mum F19:…Oh, sorry no I mean the FITNET arm. Sorry, I have a friend from a medicine profession and she describes the active arm, as in this is the active arm of the trial, and the other one is the control arm, i.e. what we already know works.*
>
> *Interview:FITNET-NHS Online CBT 14yrs Male*
>
> *[No audio of recruitment consultation.]*

> *Mum S35:…If we end up as the control group, it's a shame but you have to have a control group, and if it means that eventually the NHS go, 'Yes this is great', then, you know, someone benefits, and if people don't take part then it doesn't happen… [laughs] I'm quite gutted that we're in the control group… if it gives you your control group, it gives you your control group, then you've got your data.*
>
> *Interview:SMILE Specialist Medical Care 12yrs Female*

In contrast, during the MAGENTA and CONTRACT trials, 'standard' treatments (activity management and surgery) were more often referred to positively by parents

and perceived as potentially more beneficial for their child, as opposed to 'experimental' treatments (Graded Exercise Therapy and antibiotics) which were perceived as more risky or harmful:

> *Dad M42:…Isn't there usually an incentive to go for just the standard treatment [activity management] that's been tried on young people?*
>
> *Recruitment consultation:MAGENTA Declined trial 14yrs Male*

> *MUM CE9:…My child not gonna be like a mouse in a laboratory because… I never heard that, [antibiotic treatment for appendicitis] my child not gonna be experimental toy.*
>
> *Recruitment consultation:CONTRACT Declined trial 13yrs Male*

However, it should be noted that many young people responded positively to the prospect of doing more managed exercise in the MAGENTA trial, and were enthusiastic about increasing, or starting to do some exercise:

> *Young person M20:…And I like doing exercise…I wasn't doing any exercise because I was just so tired … so like we were saying it would be good if I start exercising.*
>
> *Interview:MAGENTA Graded Exercise Therapy 17yrs Female*

Risk of harm

Parents' perceptions of risk differed between the CFS/ME trials (SMILE, MAGENTA and FITNET-NHS) and the surgical trial CONTRACT due to the contrasting long term or acute conditions under investigation. Parents discussed a preference for the

activity management group or treatment outside of the MAGENTA trial because of online information suggesting that Graded Exercise Therapy may be harmful to someone with CFS/ME:

> *Mum M110:…The research that I've done has indicated that there may be some complications to some patients through Graded Exercise, especially, and I just don't feel that I can take the risk with my own child, I think if it was me I might give it a go, and also it is [patient name] decision obviously… I wanted her to make a decision as well and she's read through the information as well, she'd like to go down the other route.*
>
> *Recruitment consultation:MAGENTA Declined trial 12yrs Female*
>
> *[Only mum present during recruitment consultation.]*

In the FITNET-NHS trial a minority of parents were concerned that FITNET Online CBT might reinforce the condition as being psychological and not physical, but more often parents felt that psychological support in either study group would be beneficial to their child:

> *Mum F11:…It worries me that it makes it out that it's more of a psychological condition when you know, obviously if you're seeing it first hand and I know how physically it affects the body so yeah, I'll be honest that side of it [FITNET] I am probably more a little bit more concerned about.*
>
> *Recruitment consultation:FITNET-NHS Skype activity management 13yrs Female*

Preference for treatment was not raised by parents or young people during the SMILE RCT in relation to potential harm, despite a negative online campaign to stop

the trial (some patient groups were against the Lightning Process being researched in relation to CFS/ME, particularly in a paediatric setting):

> *Mum S38:…I mean looking at the information that you gave us it [Lightning Process] does seem to be more successful than other things and seems to do less harm than other things… So made worse GET… mind you CBT is quite high as well…*
>
> *Recruitment consultation:SMILE Specialist Medical Care 16yrs Female*

In the context of acute appendicitis (CONTRACT) a 'new' or 'non-standard' treatment, such as antibiotics, was seen by some parents as posing unnecessary or unacceptable risk. This contrasts the positive perceptions of 'new' treatment in the SMILE and FITNET-NHS trial (see: 'Access to treatment: A new angle, something different' and 'Active versus Control and Experimental versus Standard treatment'):

> *Mum CE7:…I think from my side of things, it's working out what the risk is to [Patient name] without the standard approach.*
>
> *Recruitment consultation:CONTRACT Antibiotics 14yr Male*
>
> *[Recurrence also treated with antibiotics.]*

> *DAD CE19:…Surgery is, you know, it is kind of the standard… intervention at the moment… when it's your child that's lying there, you want something that you know is gonna work.*
>
> *Recruitment consultation:CONTRACT Appendicectomy 11yrs Male*

During the CONTRACT RCT the antibiotic group was also seen as potentially dangerous because the appendix was being “left” which was perceived as “delaying” treatment. Parents also felt there was potential to cause more harm later because antibiotic treatment could potentially be ineffective, causing recurrence and a more advanced infection and complications:

> *Dad CE14: … I'm more inclined probably to pass at the moment and that's only because mine was left when I was young and mine actually ruptured, so I was an emergency, rushed in. And my only concern is if we leave his and it doesn't work, I don't want him to be in that same boat where it's left… and, you know, because that can become life threatening, can't it?*
>
> *Recruitment consultation:CONTRACT Declined trial 5yrs Male*

> *Young person CF21:…[?I want?] Surgery.*
>
> *Mum CF21:…You think you’d rather just have it done? …then you just know what you’re dealing with don’t you, whereas if you have, if you’ve got allocated to antibiotics then you’d have to wait to see if that worked first, and then you might still end up having it anyway.*
>
> *Recruitment consultation:CONTRACT Declined trial 15yrs Male*

More is better ‘pick and mix’ approach

Risk for those considering participation for their child in a CFS/ME trial was more focused on trial entry limiting access to treatment which might have potential to improve their child’s condition and quality of life. In the context of the MAGENTA trial combining elements of graded exercise and activity management at the same time was perceived by some families as an opportunity to get as much ‘treatment’ as

possible and was more achievable outside of the RCT. Families sometimes discussed the perception that more or using both treatments outside the trial at the same time was a better option. In MAGENTA this 'pick and mix' approach was also described by health professionals treating MAGENTA participants (see: Individual versus collective equipoise). The 'risk' of not having access to potentially beneficial treatment was therefore greater for those considering participation in the MAGENTA trial:

> *Mum M52:…We felt both approaches need to be put into place, it was too focused down one line, too limiting. Treatment offered in the trial wasn't enough, it's parts of the pieces of a jigsaw, but it's not seeing the whole picture.*
>
> *Young person M52:…I thought I needed to look at a whole range of things*
>
> *Interview:MAGENTA Declined trial 15yrs Female*

In SMILE and FITNET-NHS more was equated with 'one' of the trial groups, Specialist Medical Care plus the Lightning Process or the FITNET Online CBT group which had 'more' chapters as opposed to three skype sessions, (after feedback from interviews the number of skype sessions was increased to six when the internal pilot was converted to a main trial). The mode of treatment delivery, e.g. group, skype or email were frequently discussed in relation to preference for treatment during FITNET-NHS and SMILE consultations and interviews, as opposed to the underpinning treatment approaches, e.g. neuro-linguistic programming, activity management, or CBT. Many young people eligible for SMILE were apprehensive about the group work used to deliver the training course:

Young person F13:…I think the idea of having a set number of calls means that if it doesn't work out… I still need some more treatment. It kind of just feels a bit like 'so where do I go now?'

Recruitment consultation:FITNET-NHS Skype activity management 15yrs Female

Past experience of intervention

If a parent had experienced appendicitis themselves in the past, or had experience of a close family member being particularly ill after a perforated appendix, they often stated this as their reason for declining the trial and opting for surgery outside of the RCT:

Mum CF6:…I think the worry is, is that he's [dad] really adamant he wants the surgery. I think it's just his old-school, gut feel thing… his brother had a really bad, his brother's appendix, so I think he's just got this, like emotional.

Recruitment consultation:CONTRACT Declined trial 5yrs Female

Mum CD3:…Um, I don't think... no, I'd just rather get ?him?... Yeah, the normal way.

Recruiter CE5:…Okay, that's absolutely fine. Um, so in that case, what we'll try to do is take his appendix out, okay… We tend to do it as a key-hole procedure.

Mum CD3:…Yeah, that's how mine was, yeah.

Recruitment consultation:CONTRACT Declined trial 10yrs Male

Because activity management involved restricting activities that young people enjoyed, and manually recording them (on paper sheets or an App https://itunes.apple.com/gb/app/activeme/id458308805?mt=8)) some young people reported that they had already tried this and had not enjoyed doing it:

> *Young person M25:…I've done the sheets before… [name] gave us the sheets from the [local hospital] so I had to colour those in, and that was just a bit time consuming, to be honest [laugh].*
>
> *Interview:MAGENTA Graded Exercise Therapy 16yrs Female*

Anxieties about treatment and treatment delivery

Anxiety about treatment mode (e.g. group work, lack of face-to-face contact) or the treatment itself (e.g. Graded Exercise Therapy or a surgical procedure), were factors which young people (and some parents) considered important in relation to their preferences for trial treatments. Parents of children considering CFS/ME trials reported searching for evaluations of CFS/ME treatments online from non-NHS sources. For young people eligible for the SMILE and MAGENTA RCTs it was fear or apprehension about the prospect of having to do something they didn't want to do, either group work in the Lightning Process (SMILE trial) or 'exercise' in MAGENTA trial.

The Lightning Process was delivered in a group setting, and this was the main apprehension young people had about participating in the RCT. One of the two SMILE patients who declined the trial after the recruitment consultation expressed a preference for specialist medical care because she had considerable anxieties about social situations and did not want to meet new people or participate in group work:

Patient S18:…Do I have to do the course, like where you like go and meet people, or can you just do the questionnaires?

Recruitment consultation:SMILE Declined Trial 16yrs Female

Some young people and parents considering the MAGENTA trial felt that they, or their child would simply be unable to follow the Graded Exercise Therapy treatment pathway because the level of 'exercise' required would be too much for them:

Young Person M57:…I wanna do the research but I don't really want to do the graded exercise, because of the 50:50 chance of doing that, so I think I'd rather just not be in the study.

Dad M57:… Because we know it's a 50:50 chance, he's not prepared to take that risk.

Recruitment consultation:MAGENTA Declined trial 16yrs Male

Mum M140:…[Graded Exercise Therapy] wasn't a route he wanted to go down… I think he's researched this quite a lot.

Recruitment consultation:MAGENTA Declined trial 16yrs Male

[Only mum present.]

Some families declined the FITNET-NHS trial during the internal pilot phase of recruitment because they preferred face-to-face treatment outside the trial (24/48 50%). During the recruitment consultation, recruiters either offered face-to-face treatment or discussed waiting times and families stated, *"I think we probably need to have a bit more of talk about it"* and the recruitment consultation ended:

Mum F8:…Could I just ask if she decides not to go ahead with the study and we come for face-to-face appointments at [location] how regular would they be?

Recruitment consultation:FITNET-NHS

[Declined trial and opted for face-to-face appointment.]

Other families mentioned a preference for face-to-face treatment but still opted to participate in the trial, it was unclear whether this was due to difficulties with accessing treatment locally or differences between parent and young person preference:

Mum F22:…Me personally, I don't like it [skype] because I'm highly old fashioned. I like to go into a room and I like to talk to somebody … and that's it. But that's just me…

Researcher 8:…What about you [patient name]? Did you think it could work being treated over Skype?

Young Person F22:…Yeah. [inaudible comment].

Interview:FITNET-NHS Skype activity management 11yrs Female

Many of the young people eligible for the CONTRACT trial were apprehensive about surgery. Parents often expressed preference for antibiotics on their child's behalf, because of anxiety and fear of the prospect of an operation:

Young person CD14:…[Speaking very quietly] I don't want an operation.

Recruitment consultation:CONTRACT Appendectomy 8yrs Male

[Withdrew from trial.]

Dad CE25:…I mean…he's saying he's not too bothered but… he would rather...you know, not have the operation.

Recruitment consultation:CONTRACT Antibiotics 9yrs Male

[Treatment failure - revert to surgery.]

Misunderstandings: Evidence-based treatment and therapeutic misconception

A minority of parents in the MAGENTA and FITNET-NHS trials had misperceptions about one of the treatment groups in the study, believing that activity management was evidence-based:

Dad M42:…Just for clarification, I think [health professional] talked a bit about this, the graded exercise therapy, is the treatment that isn't standard treatment for young people at the moment… the dis-incentive of that isn't there, with the little evidence that graded exercise therapy works well with young people at the moment, cos the study hasn't been done…

Recruitment consultation: MAGENTA Declined trial 14yrs Male

There was no audio-recording of the conversation between 'Dad M42' and the health professional he spoke to at his child's initial assessment (see: Missing conversations from the consultation process). A FITNET-NHS mum discussed her preference for the activity management group, not because of an existing evidence-base but because it involved face-to-face interaction, despite there being no evidence that face-to-face treatment was more effective:

Mum F13:…One of the things I thought was an advantage of this arm [activity management] …you have the sort of face-to-face interaction over Skype...I suppose I always tend to think that face-to-face interaction is nicer and more helpful.

Recruitment consultation:FITNET-NHS Skype activity management 15yrs Female

One CONTRACT parent expressed a belief that her son had been randomised to the antibiotic treatment group because that was the most appropriate treatment for him personally given his clinical diagnosis. In contrast her son appeared to understand randomisation as a chance of receiving antibiotic treatment via the trial, *"without doing the trial I would definitely had to have had the operation" [Participant CE7].*

Mum CE7:…No, that's interesting 'cause obviously that's maybe a lack of understanding on [patient name] side because I think the, [surgeon 1 name] and [surgeon 2 name] had been saying look we're going to try this antibiotic approach because we think that's the right thing to do, but you do have a choice if you want to have an operation and not to do that. So that was a care thing, wasn't it, rather than the actual trial itself?

Interview:CONTRACT Antibiotics 14yrs Male

[Recurrence also treated with antibiotics]

Altruism

All participating families (young people and parents) discussed altruistic reasons for trial participation:

Mum S35:… I do actually really believe in research, and I understand the point … cos you'll never get the NHS to fund it unless you can prove it to

them that it's worth it… even if we don't get to do it, if we end up as the control group, it's a shame but you have to have a control group, and if it means that eventually the NHS go, "Yes this is great", then, you know, someone benefits, and if people don't take part then it doesn't happen.

Interview:SMILE Specialist Medical Care 12yrs Female

Mum F19:…[Participant] felt quite excited when he realised he could get on with the trial, and I guess help others in the future as much as he'd like to make sure he gets better as well.

Interview:FITNET-NHS Online CBT 14yrs Male

[No audio of recruitment consultation.]

Young Person CD9…'cause like I think the next person [in the future] who got this might be able to go on to antibiotics and it would help them even more if there was a better method of getting rid of it.

Interview:CONTRACT Antibiotic 12yrs Male

Some young people discussed altruism and their interest in science as overriding reasons for taking part:

Young person M43:…I didn't really mind really whichever way it went…the research would sort of help people in the future...any of the outcomes were positive…. I mean doing the science subjects that I did, biology and psychology and doing studies about, research studies… I was quite sort of eager to take part in one.

Interview:MAGENTA Graded Exercise Therapy 17yrs Male

Equipoise, language and misperceptions about treatment

Analyses of recruitment consultations showed that some of the language used by health professionals when discussing the SMILE, MAGENTA, FITNET-NHS and CONTRACT did not convey equipoise between treatment groups. In the SMILE RCT there were frequent examples where the Lightning Process was described favourably e.g. *"we're getting good anecdotal evidence that it's helpful" [Family 7],* "*it's called the Lightning Process… is because some people have rapid results" [Family 37].* In contrast, Specialist Medical Care was described as *"normal medical care" [Family 8] and* families were told their child would *"just carry on as you are" [Family 11].* When reassurance was offered families were told that if randomised to this trial group they would still be receiving *"some treatment" [Family 37],* or "*you would continue to get the care you would receive anyway" [Family 72].* On occasions the Lightning Process was framed as a "*new process" [Family 73].*

> *Recruiter S2:…One group which will have the umm, normal medical care with the chronic fatigue service.*
>
> *Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 16yrs Female*

Similar language was also apparent in early consultations in the CONTRACT RCT, where surgery was framed as a known entity, "*what we usually do*" *[Family CF16] "the…previous normal treatment"* and antibiotic treatment was framed as something which was being tried or tested *"the experimental side" [Family CE16]*. Language used framed the trial as investigating whether antibiotics *"on their own"* are *"as good" [Recruiter CE8]* as having an operation:

Recruiter CE10… If you decide oh no, I don't want to have all of this done, I don't want to go to all this trouble, I would like to go the old…I would like to do it the standard way, at the moment our appropriate, our standard way would be at the moment, is to go for an operation.

Recruitment consultation:CONTRACT Declined trial 8yrs Male

Training points CONTRACT:

Alternative and neutral language to explain surgical and antibiotic treatment groups were discussed in the second training sessions:

Operative arm	Non-operative arm
Gold standard X X X Normal treatment X Normal pathway X Standard treatment X Appropriate way X	Experimental X X X Just antibiotics X
Alternatives….	
Surgery treatment? Operation?	Antibiotic treatment? Medicine (without an operation)?

After training there were more instances of recruiters using these alternative 'neutral' terms to present trial groups. This was accompanied by a statement about both approaches having pros and cons and a link to the study rationale:

Recruiter CE3:…What we know is there are two ways of treating children like this with appendicitis. ***The first is with antibiotics****, okay, given through the drip for a day or two, followed by a longer course of antibiotics that can be taken at home. Once we're sure that he's responded to the antibiotics and is getting better… and* ***the second way is an operation*** *to take the appendix out, right and* ***they both***

***have risks and they both have benefits**, and because of that we're doing a research project to compare the two…*

*Recruiter CF11:…One is with **an operation** and that's something that we've usually done, and the other way is **with antibiotic treatment**. Okay? And that's with antibiotics through a vein, and these two treatments **both work well** and we want to know which of them **works best in simple appendicitis** treatment…*

Training re-iterated the emphasis on uncertainty about the most effective treatment. That despite appendectomy being used widely in practice, antibiotics were now more effective and reliable which highlights rationale for the trial:

Recruiter CE4:…Maybe like 50 years ago, everybody was getting an operation, but now we know there are more options and… we want to see which one's best…

Some of the language used in early recruitment consultations during the MAGENTA and CONTRACT trials also suggested that involvement would be burdensome:

Recruiter M1:…Have you had the information sheet you were given at your appointment…it's quite a lot…

Recruitment consultation:MAGENTA Declined trial 14yrs Female

Recruiter CE9:…So the way it works is if you agree to go ahead with the study, um, we have lots of paperwork…

Recruitment consultation:CONTRACT Declined trial 5yrs Male

Interviewed families reported that they valued the opportunity to take part in research and appreciated being followed-up in CONTRACT, so these findings were fed back to those recruiting:

> *Young Person CE7:…I'm very pleased I've done that, yeah, just to help out and not have to have an operation was also quite a good bonus.*
>
> *Interview*:CONTRACT *Antibiotics 14yrs Male*
>
> *[Recurrence also treated with antibiotics.]*

> *Mum CF9:…It was a sort of selling point, wasn't it… for the study… that you get this extra follow-up.*
>
> *Interview:CONTRACT Appendectomy 8yrs Female*

In early consultations recruiters in the MAGENTA and FITNET-NHS RCTs recruiters consistently framed the RCTs as restricting choice, not providing a way in which to make a decision about treatments in an area where there was uncertainty about the effectiveness of treatment, and reinforcing trial rationale:

> *Recruiter M1:…So if you decide to be in the study, we will randomly allocate you to one of the groups so that means you can't choose which group you're in…*
>
> *Young person M109:…Alright*
>
> *Recruiter M1:…Okay, so There's a 50% chance you'll be in the graded exercise therapy group and a 50% chance being the activity management group okay?*
>
> *Young person M109:…Alright.*

Recruiter M1:…So you can't choose which group….

Recruitment consultation:MAGENTA Graded Exercise Therapy 17yrs Male

This also occurred in the CONTRACT trial, but it was not the recruiter, but the research nurse who highlighted lack of choice:

Research Nurse CE1:…Just to say obviously you won't be able to choose your treatment option [laughs].

Mum CE10:…No.

Recruitment consultation:CONTRACT Declined trial 8yr old male

Training points Randomisation:

Information relating to how randomisation would be carried out had been provided in early recruitment consultations but why randomisation was used was not discussed as frequently with families. After training there were more examples of recruiters explaining why randomisation was used:

Recruiter CE14:...Obviously we don't choose who gets which treatment, because in order to have two groups of children that are the same, they have to be randomised. So they have to have a fair chance of getting either treatment. Otherwise if we pick what treatment they get, it might be that we give sicker people antibiotics or we give more well people an operation...

There were instances in the MAGENTA and FITNET-NHS trials when recruiters stated how pleased they were when families were randomised to their 'preferred' treatment:

Recruiter M1:…Okay, now you have been allocated to the graded exercise therapy group…

Young person M109:…Okay.

Mum M109:…That's what he wanted.

Young person M109:…Yeah.

Recruiter M1:…That's good news.

Recruitment consultation:MAGENTA Graded Exercise Therapy 17yrs Male

Recruiter F10:…So you have been allocated to the online CBT arm, the FITNET.

Mum F16:…Okay.

Recruiter F10:…How do you feel about that?

Mum F16:…Fine, no fine, he will be absolutely fine.

Recruiter F10:…Great…I think it will be a good fit for you as well. I think either arm you would have done fab in, but I personally, I think that this can be quite helpful because some of the bits that you have both been saying over this phone call.

Recruitment consultation:FITNET-NHS Online CBT 16yrs Male

During the MAGENTA and FITNET-NHS trial some consultations reinforced certain misperceptions that parents had about trial involvement. In the MAGENTA trial this included a perception that outside of the trial more treatment was available to young people with CFS/ME, who would be offered "*a bit of everything*". The recruiter did not highlight the rationale for the study or current lack of evidence base for treatment delivered outside the trial:

> *Dad M32:…It's just purely that we didn't want to exclude any element of the package that [health professional] had spoken about….*
>
> *Recruiter M1:…If you decide not to go into the trial we will arrange an appointment as soon as we can…which will set up a programme, it will involve some activity management, possibly some Graded Exercise Therapy, as you said, the whole package if you like, absolutely every programme we set up is individualised. If you decide to go in the study, 50% of the children will be allocated to activity management and 50% to Graded Exercise Therapy.*
>
> *Recruitment consultation:MAGENTA Declined trial 13yrs Male*

> *Recruiter M1:…We'd be asking you to do that amount of activity, if you're in the study that would be either activity management or Graded Exercise Therapy, if you decide not to be in the study it will be a mix of everything kind of thing.*
>
> *Recruitment consultation:MAGENTA Declined trial 13yrs Female*

Training points MAGENTA:

During MAGENTA families had concerns that doing one or the other treatment might not be as effective as doing a combination of the two. There was little change in the presentation of information when parents raised this concern during recruitment consultations, although after training the recruiter sometimes highlighted trial rationale:

> *Recruiter M1:…If you're in the study you'll be randomly allocated to either be in the Graded Exercise Therapy group or the activity management group… the reason we're comparing these two groups is because we're already using these treatments and we want to know if by concentrating on one of these treatments children will do even better*

The recruiter also highlighted that families were "*free to look up other information"* themselves, e.g. if randomised to activity management they could manage physical activity themselves without guidance:

> *[2 minutes into conversation]*
>
> *Recruiter M1:…We want to know if concentrating on one treatment is better than doing a bit of everything….*
>
> *[15 minutes into conversation]*
>
> *Mum M69:…What I'm meaning is you know if she's in one group as opposed to the other group will there be things that she won't have access to in terms of what you think…..*
>
> *Recruiter M1:…If you don't do the study you'll get a little bit of everything, but the difference with being in the study is that you know, whichever group you're in, the emphasis will be on one or the other, but obviously you're free to look up other information, but from the clinician*

who's seeing you's point of view, their treatment and advice will be focusing on one or the other, the general information about managing chronic fatigue syndrome is the same in both groups but the actual specific treatment will focus on either the activity management or the graded exercise therapy…

Recruitment consultation:MAGENTA Declined trial 17yrs Female

Suggestions put forward during training which were not put into practice included:

- Consistently discussing equipoise and the current lack of evidence-base for treatment interventions.
- Discussing the potential burden of using activity management and Graded Exercise Therapy techniques. Using 'both' approaches would involve the patient 'monitoring' and 'restricting' physical and cognitive activities, when it may only be necessary to monitor/restrict either cognitive or physical activities to see improvement in symptoms of fatigue.

In a minority of FITNET-NHS consultations there were connotations that face-to-face treatment outside of the trial was the 'gold standard', implying any treatment offered in the trial via Skype or Online CBT would be less beneficial:

Recruiter F1:…Well, I mean, the best thing you can have is a face-to-face appointment… is being near enough to a local specialist service that can give you the support and help and advice you need to get better in our opinion.

Recruitment consultation:Exclusion local specialist service

In the extract below the recruiter has just explained each treatment option available in the RCT, (activity management via Skype and Online CBT) the family have not asked about face-to-face treatment but this is still discussed as the benchmark for treatment which is used in the gold standard delivery mode:

> *Recruiter F10:…Like I said, they're both the approaches we use face-to-face, so we know they're good.*
>
> *Recruitment consultation:FITNET-NHS Online CBT 16yrs Female*
>
> *[Randomisation outcome discussion not audio-recorded.]*

At times recruiters appeared to struggle with the concept of conveying equipoise throughout the recruitment consultation, stating after the families group allocation had been given, that they were 'secretly hoping' they would be randomised to the treatment they had stated they preferred earlier in the recruitment consultation:

> *Recruiter F12:…So you have been randomised into the FITNET NHS, online CBT arm.*
>
> *Mum F7:…Oh yes, ideal.*
>
> *Recruiter F12:…Yes, I was secretly hoping you would be because I know you guys have a preference…*
>
> *Recruitment consultation:FITNET-NHS Online CBT 14yrs Male*

Equipoise between treatment groups within the FITNET-NHS trial was not always communicated effectively during recruitment consultations. The name of this trial may have made this particularly difficult for recruiters because it appeared to mention only one treatment group 'FITNET' (Online CBT), although 'NHS'

represented the activity management (Skype) group. In the extract below the participant's father perceived FITNET Online CBT to be the active group, *"the effective route for helping people suffering from CFS",* that was being compared with, *"an alternative"* treatment used to *"verify whether the CBT is more effective".* The recruiter does not address this perception of lack of equipoise between treatment groups, and tells the dad, "*that's it, in a nutshell*" positively affirming this rationale for the RCT as correct. The recruiter does go on to state, *"they're both good standard approaches that we currently use in our specialist service"* and also highlighted: *"we don't know which of those treatments is best"* but closed this section of the conversation by again confirming dad's perception of the RCT. This recruiter did not acknowledge that the meaning the dad has assigned the 'Skype' activity management group was one of 'control' comparator: *"as you said, it's which one of these works better":*

> *Dad F12:…The study's going to look at the effect of whether CBT, online delivered CBT, is the effective route for helping people suffering from CFS and if that will improve their condition. That has to be done against two sets of criteria. One where there's CBT and one where there's an alternative put forward to verify whether the CBT is more effective than the alternative.*
>
> *Recruiter F10:…Lovely, yeah, that's fab. So that's in a nutshell, that's it really. So there's the two arms to the study. The FITNET NHS study is comparing the two treatments for children and young people with CFSME who don't have access to a local specialist service... We use both of those with our face-to-face patients to treat CFS/ME, but we don't know which of those treatments is best, is more helpful for young people to help them recover, and that's why we're doing the study. As you said, it's which one of these works better and also can we adapt them to do them over the internet for people who can't have that face-to-face service*

Recruitment consultation:FITNET Online CBT 16yrs Female

CFS/ME health professionals delivering treatment had a preference for face-to-face appointments which they felt were superior, since *"maybe they're [families] not getting as much of a package as they perhaps would [Health Professional FR]"* if they were seen face-to-face as opposed to in the trial via Skype or Online delivery:

> *Health Professional FR:…Yes so naturally I probably would have a preference to see them face-to-face 'cause I kind of get how they walk, how they come in, how they just hold themselves and their posture… [Interview]*

Because of the nature of the condition, and an existing evidence base in adult trials, the CONTRACT trial was the only trial in which recruiters used figures in discussions of risk. Although most CONTRACT recruiters reported feeling confident about using communication techniques to balance families' treatment preferences before any training had taken place, analysis of early recruitment consultations identified that although both treatments were discussed, the risks of surgery were minimised. Recruiters discussed the risks of surgery less often and in a more general way than antibiotic treatment, and omitting numeric figures that represented the risk of complications:

> *Dad CF21:…Is there a high risk of getting an infection from the surgery?*
>
> *Recruiter CF15:…Is there a high risk, no.*
>
> *Recruitment consultation:CONTRACT Declined trial 15yrs Male*

Figures in relation to the risk of complications related to having surgery were only presented in seven consultations during the whole 12 months of recruitment. Surgery was often communicated as "*an operation that we do routinely and is very safe*" *[Family F18]:*

> *Recruiter CD19:…So they would be, erm, damaging something inside the tummy, erm, is very rare. We think it's less than 1 in 1,000…*
>
> *Recruitment consultation:CONTRACT Appendectomy 11yrs Female*

During the CONTRACT recruitment consultations, figures relating to the risk of antibiotic treatment failure and recurrence when treated with antibiotics were communicated in 51 consultations, and the use of figures to represent the risk of future appendicitis recurrence varied:

> *Recruiter CE2:…There are risks during those operations that we can cause damage doing that… you can get infections…so we know that most patients with sort of an appendix mass or complex appendicitis… I think about **85%** will be successfully treated in their first… presentation of that. And of the ones that are successfully treated, about **a quarter** of them will need to have…appendicectomy in the future*
>
> *Recruitment consultation:CONTRACT Antibiotics 14yrs Male*

Training points CONTRACT:

After discussion (during the third training session) about the way in which figures were being presented to families about the risk associated with antibiotics but not the risks associated with surgery some recruiters began to discuss surgical risk

with supporting percentages or figures:

> *Dad CF11:...Why are you trialling this system? What do you think are the possible benefits of going that route rather than the traditional route of just getting the appendix out?*
>
> *Recruiter CF11:…Well some, some parents, erm, would rather not have surgery...because surgery isn't without fail. Surgery does have complications, and you're looking at around 25% of, erm, patients who have an appendicectomy have complications related to that.*
>
> *Recruitment consultation:CONTRACT Appendectomy 13yrs Male*

Examples of good practice from phase two recruitment also highlighted the way in which antibiotic treatment could be discussed in terms of the 'success' instead of 'failure' rate:

> *Dad CF20:…Well I think my first concern obviously is if you do with the antibiotics, does that mean that it can come back again?*
>
> *Recruiter CFS11:…I described it being at one in seven children who are treated that way [with antibiotics] would have that recurrence…but that's a six in seven chance of success which is pretty good.*
>
> *Recruitment consultation:CONTRACT Antibiotics 7yrs Male*

Although the risk of recurrence and treatment failure were discussed more frequently throughout trial recruitment, there were slight changes in the way that recruiters communicated the risks of surgical treatment for appendicitis during the

later stages of recruitment, with examples where surgical risk was presented with figures to clarify risk:

> *Recruiter CF14:…20% of the people having an operation may have complications, not all of them are major*
>
> *Recruitment consultation:CONTRACT Appendectomy 7yrs Male*

There were times during the CFS/ME trials when recruiters didn't give young people and parents time to respond to points they had made or questions that recruiters had asked which might have resulted in a discussion about preference for treatment:

> *Recruiter M1:…Okay…you don't mind which group you go in to? Cos that's the way it is, it's just a chance [recruiter doesn't cede the floor] I put your age and umm, whether you're a girl or a boy into the computer and then I press the recruit button and the computer decides which group you're in, okay, so that's how we randomly allocate you to one of the groups.*
>
> *Recruitment consultation:MAGENTA activity management 13yrs Female*

When this family were given their allocation, it was apparent they had a preference which had not been discussed:

> *Young person M88:…That's the one I wanted anyway…*
>
> *Mum M88:…Yay… [both laugh].*
>
> *Recruiter M1:…Oh I'm so pleased.*
>
> *Recruitment consultation:MAGENTA activity management 13yrs Female*

Recruiter S4:…There'd be a little presentation, a bit of group work, how does that sound [patient name]? [recruiter does not cede the floor]… Would you be alright with that? [recruiter does not cede the floor] … Sitting in a group, they might ask you a few questions, in a little group. Anything you don't wanna do you just say you don't wanna, you know. They give you up to half an hour of homework a day, but that is to help you take in what you've learnt….

Mum S73:…Yeah.

Recruitment consultation:SMILE Specialist Medical Care plus Lightning Process 14yrs Female

[Participant did not attend Lightning Process course.]

Recruiter F10:…Thinking about the two different arms, do you have any kind of preference? [recruiter does not cede the floor] Though, as I said, I don't choose and you don't choose, but if you could choose would you have a preference for which one of the arms you'd go into?

Young person F12:…Hmm... I... No, not particularly. I don't mind.

Recruitment consultation:FITNET-NHS Online CBT 16yrs Female

In other consultations, the recruiter did not respond to misconceptions about treatment:

Young person F13:…I suppose at first I was a bit suspicious of the fact it's all over the Internet [Online CBT]. That is a strange idea, to me

Recruiter F1:…Right okay.

Recruitment consultation:FITNET-NHS Skype activity management 15yrs Female

In the following example, the recruiter did not balance this information by providing similar information about the Online CBT group, which is also a treatment delivered 'face-to-face' by the specialist CFS/ME service. Later in the consultation the recruiter did go on to explain that, *"FITNET one is over the internet, and although you may not see the person you do develop a personal relationship with that person because you're sent, they will be sending you personal emails".* Although the young person acknowledges this with a "*yes*" she re-iterates during a later interview discussion that she was still unclear as to whether she would have been speaking to a "*real*" person if she had been randomised to the FITNET Online CBT, or was it just "*an online computer system*" without input from a health professional:

> *Young person F13:…I was quite glad that I'd actually be speaking to someone [via Skype]. In the sense that I was never sure with the other one whether I would be speaking to someone or if it would all just be an online computer system.*
>
> *Interview:FITNET-NHS activity management via Skype 15yrs Female*

Training points FITNET-NHS:

In the FITNET-NHS trial language was changed to reflect fact that both approaches were 'standard':

> *Recruiter F1:…Both activity management and cognitive behavioural therapy are both currently used in our service. Up to now they are mostly delivered face to face in a clinic here in [city]. They are both good and standard treatment approaches for the treatment of chronic fatigue, but as I said, we don't know if one is better than the other.*

Recruiter F12:…We don't know which is better, otherwise if we knew which is better that's the one we would be offering everyone.

5.3.3 Understanding how recruiters respond to treatment preferences in paediatric trials

This section reports themes which were developed from analysis of the ways in which recruiters communicated to elicit preference, explored and responded to treatment preferences during consultations. This involved the analysis of recruitment consultations before and after training had taken place in each of the recruiting trials. Of interest was the way in which recruiters identified and responded to families' preferences. Two commonalities were identified across the four trials:

1. Recruiters accepting preferences raised by parents and patients at face value.

2. Recruiters used language that may have created or reinforced existing preferences and did not convey equipoise.

Acceptance of preference and missed opportunities to explore preference

During the early months of recruitment to the MAGENTA and CONTRACT trials, recordings of recruitment consultations highlighted that when parents expressed preferences for treatment, these views were often accepted at face value. Expressions of parental preference in the MAGENTA trial focused on preferences for activity management due to negative perceptions of Graded Exercise Therapy:

Recruiter M1:…In which case it [Graded Exercise Therapy] probably isn't, it isn't suitable then, because you are completely randomly allocated…

Recruitment consultation:MAGENTA Declined trial 14yrs Male

Recruiter M1:…I think if you do have a strong preference it's probably not the best thing to do at the moment…

Recruitment consultation:MAGENTA Declined trial 15yrs Female

Training points MAGENTA

Some parents had concerns about their child using Graded Exercise Therapy (see also: Risk of harm). Using anonymised extracts from the MAGENTA trial, training highlighted: open questioning, equipoise, discussing what GET/AM interventions involve, lack of evidence-base. After training sessions there were observed changes in recruiters' communication practice in response to parents' negative perceptions of Graded Exercise Therapy, with more examples of open questions and attempts to correct misperceptions that Graded Exercise Therapy would require the participant to do high levels of exercise:

Young person M3:…It's the exercise one I don't really like the sound of

Recruiter M1:…Graded Exercise Therapy doesn't mean that you've got to go and do, sort of a jog round the block, it doesn't mean that you have to start working out at the gym more, doing loads of umm, high level activity…we're not talking about [laughs] you know getting to Olympic athlete standard, you know a programme to build you up like that, we're talking about just, you know just focussing on you, what is appropriate exercise for you and to build that up for you as an individual, little by little…

Recruitment consultation:MAGENTA Graded Exercise Therapy 14yrs Male

Mum M49:…I think he was worried about being picked for the exercise one.

Recruiter M1:…Don't be frightened by that, you know, we're all different and, think of it as physical activity rather than exercise… we take the amount of physical activity that you're able to do on good days now and use that as a baseline on which to build…

Recruitment consultation: MAGENTA Graded Exercise Therapy 15yrs Male

Recruiter M1:…So it doesn't mean that you are gonna be asked to do circuit training or jogging or anything like that [both recruiter and participant laugh] umm, okay, it's just the name of the treatment…

Recruitment consultation:MAGENTA Graded Exercise Therapy 17yrs Female

Surgery was often the preferred treatment for parents in CONTRACT, because of the perceived urgency of "*getting on*" with treatment, and the risks of further deterioration, a "*burst*" appendix or recurrence in future. Some parents also raised their own experiences of appendicitis in the past (see also: Past experience of treatment), or wanting their child to be treated "*the normal way*" and these were important factors which resulted in many parents declining the trial for their child:

Mum CE16:...I just wanna get him sorted.

Recruiter CE5:…Yep, fair enough. So you just want to go and have surgery you think?... Fair enough.

Recruitment consultation:CONTRACT Declined trial 10yrs Male

Mum CF16: …I spoke to my family and that's the...main

Recruiter CF11: okay…that's fine…okay, in that case that's okay, we will use... the usual treatment that we would do, okay.

Recruitment consultation:CONTRACT Declined trial 13yrs Female

Recruiter CD5:…Do you want to know a bit more about it?

Mum CD3:…Um, I don't think... no, I'd just rather get ?him?...

Recruiter CD5:…You'd just rather get on?

Mum CD3:…Yeah, the normal way.

Recruiter CD5:…Okay, that's absolutely fine.

Recruitment consultation:CONTRACT Declined trial 13yrs Male

At times during the CONTRACT trial recruiters explored preference but then appeared to 'accept' that families had a preference and often left them 'to think about it' on their own, without input from the recruiter. Since audio-recorders were usually turned off at this point in the conversation it is not known whether recruiters offered any further information to balance treatment groups or challenge preference:

Dad CD11:…He said he wants the op though, he doesn't want to go for the antibiotics.

Recruiter CD3:…You don't want to go for the antibiotics?

Young Person CD11:…Yeah, that's what me mum said 'cause we're flying in 12 days.

Recruiter CD3:…Cause you're going on holiday?

Dad CD11:…It's up to you how you wanna do it?

Recruiter CD3:…And you don't have to make a decision immediately. We kinda give you all this...information and then, we can give, half an hour, an hour or so. You're not, you're not gonna go to theatre in that time...

Recruitment consultation:CONTRACT Declined trial 13yrs Male

Training points CONTRACT:

Equipoise and exploring preference for surgical treatment.

Using anonymised data extracts during the CONTRACT trial training: Encouraged recruiters to explore families' reasons and beliefs in relation to preference for treatment and trial participation, instead of accepting preferences for surgery at face value. There were examples of recruiters reassuring parents that their child was eligible for the trial because they had 'simple' appendicitis and they would be closely monitored and cared for:

Recruiter CE14...We now know that for people who've got a simple appendicitis, so you've probably heard burst appendixes and those sorts of things, it's not how [patient name] appears at the moment. There's no evidence to support that… so if someone like him, an option to avoid a general anaesthetic and an operation would be to give him antibiotics only… and that is… we know as a safe alternative to just putting you to sleep and offering you an operation, basically.

Recruitment consultation:CONTRACT Antibiotics 9yrs Male

The majority of parents had some concerns about their child's appendicitis being treated with antibiotics (see also: Risk of harm) particularly if they, or a close family

member had, had a bad experience of appendicitis in the past. Training encouraged recruiters to emphasise that both treatments were good options, both had pros and cons, hence the reason for the trial:

> *Dad CF20:…I've had it myself, I know how...painful… I don't want him to go through that again, you know what I mean? Now with the surgery... it ain't coming back.*
>
> *Recruiter CF11:…Yeah, that's certainly a valid view and a valid apprehension… certainly a fear that parents have but it's still a good chance of it being managed effectively... in the recent past there have been lots of studies because parents have wanted an option to surgery…*
>
> *Recruitment consultation:CONTRACT Antibiotics 7yrs Male*
>
> *Recruiter CE5:…Um, I think I can assure you that whatever we do, you'll be very closely looked after, um, and [patient name] will be very well cared for.*
>
> *Recruitment consultation:CONTRACT Declined trial 10yrs Male*

These conversations did not always result in consent to the trial (particularly where one parent was not present for the recruitment consultation) but more recruiters were introducing the concept of uncertainty about which treatment was most effective:

> *Mum CF18:…So even if he takes antibiotics and it comes back you have to operate… Whichever is best for him, I'd like you to tell me because you know more...*

Recruiter CF17:…I can understand what you're saying...you're saying, look there's that element of uncertainty and you want to ask me what do I think's... best.

Recruitment consultation:CONTRACT Declined trial 13yrs Male

Recruiter CE14:…So and the reason we're talking about it is because we don't actually know which is the better thing to do… we routinely would, in the past, do an operation, take it out but in adults and children we know that there is an alternative that is safe and avoids an operation and avoids an anaesthetic…

Mum CE1:…He needs antibiotics anyway. Like you say, you won't be able to operate on him today anyway, so it would be tomorrow and that's a good 24 hours away…

Recruitment consultation:CONTRACT Appendectomy 13yrs Male

Recruiters' responses to expressed preference was slightly different during early FITNET-NHS consultations, mainly because families did not always express preferences as directly or clearly before randomisation in this trial. FITNET-NHS recruiters also used closed questions when asking about preference, therefore missing opportunities to explore and discuss preferences. Young people generally stated they were willing to accept *"whichever one" [young person F13]*. With parents stating they felt treatments would *"help either way" [mum F6].* Recruiters accepted neutrality at face value and responded to it positively, *"Great", "Lovely", "brilliant", "that's really good to hear"* discouraging families from expressing or discussing preference further. Recruiters sometimes highlighted that having a preference for treatment *"wouldn't be a problem",* but often moved on to another relevant point for

discussion in relation to the trial, without ceding the floor to explore preference further:

> *Recruiter F10:…Thinking about the two different arms, do you have any kind of preference? Though, as I said, I don't choose and you don't choose, but if you could choose would you have a preference for which one of the arms you'd go into?*
>
> *Young person F12:…Hm... I... No, not particularly. I don't mind.*
>
> *Recruiter F10:…Great. How about you, [dad's name]? Do you feel the same?*
>
> *Dad F12… I'm easy. Really, anything that... Everything has a value. The support, whatever shape or form, whatever it comes in is going to be helpful.*
>
> *Recruiter F10:…Lovely. That's really good to hear. Obviously if you did have a preference for one or the other that wouldn't be a problem, it would just be something to bear in mind that you may not get the one you were after, but it sounds like, actually, you'd both be happy with either.*
>
> *Recruitment consultation:FITNET-NHS 16yrs Female*

Families F12 and F6 who did not express preferences for treatment during recruitment consultations appeared to have been in equipoise, but interviews confirmed that both parents had not discussed their preferred treatment during the recruitment consultation:

> *Dad F12:…The element that was missing in [patient name] treatment was the [FITNET Online] CBT side… and you know it seemed to me that was something that [patient name] didn't have and that could have a very positive impact.*
>
> *Interview:FITNET-NHS Online CBT 16yrs Female*

Mum F6:…I was hoping we were going to get the FITNET [Online CBT]

Young person F6:…I didn't really mind because I didn't mind which one it was… I was fine with it.

Interview:FITNET-NHS Online CBT 13yrs Female

[Mum and young person interviewed separately.]

Training points FITNET-NHS

Equipoise and missed opportunities to offer balanced information.

Training session one used the 'Recruitment Tips' document and highlighted ways in which recruiters could encourage parents and young people to discuss their preferences e.g. '*What were your thoughts when you first heard about the study/treatments*?' (Appendix 5: FITNET-NHS: Tips for Recruitment and informed consent). Training session two provided examples of good practice, particularly in relation to using open questions to explore potential for preferences (e.g. *What do you think about treatment?*) without suggesting families should have a preference (e.g. *Do you have a preference for treatment?):*

Recruiter F1:…How do you feel about those two treatments?

Young Person F5:…Yeah, okay.

Recruiter F1:…You feel okay?

Young Person F5:…I quite like the Skype one.

Recruiter F1:…You like the sound of the skype one, is there any reason for that?

Young Person F5:…Umm, I don't know, it just sounded better.

Recruiter F1:…It sounds better, why do you think that sounds better than the other treatment?

Young Person F5:…Umm, because it's more individually face-to-face, well as face-to-face as it can be over the Internet, that's sort of good.

Recruiter F1:…Yes, as face-to-face as it can be over the Internet, yes I understand that. With the other group, with the CBT, you will have an individual clinician delivering your treatment, delivering your care and you will have a lot of communication with that individual so you will have an individual relationship with the clinician giving the FITNET treatment [online CBT) as well.

Recruitment consultation:FITNET-NHS Skype activity management 15yrs Female

When families expressed preferences there were examples of recruiters providing information about the *opposite* treatment group, to balance perceptions of treatment:

Mum F4:…But if there was a choice I'd prefer the CBT approach…

Recruiter F11:…Yeah I appreciate that the CBT has sort of different strengths to the activity management in terms of looking at how your coping with the chronic fatigue, but that's also something which… when you have the face-to-face contact with the therapist they will problem solve… how you're dealing with the activity management plan and what's getting in the way… so there will be that side of things.

Recruitment consultation:FITNET-NHS Skype activity management 13yrs Male

Recruiters also emphasised the need to be accepting of both treatment groups:

> *Mum F3:…I don't know if it's right or not, but the other one, [Online CBT] I don't know that more… geared towards someone who is a bit more down in themselves and all that kind of thing…*
>
> *Recruiter F11:…Well I mean both of the treatments will focus on what your goals are [child], if your goals are to get back to swimming and stuff like that, then both of them will focus on that.*
>
> *Recruitment consultation:FITNET-NHS Skype activity management 14yrs Male*

SMILE was the only trial which used researchers to recruit, not health professionals who were part of the clinical teams also delivering treatment to participating young people. For this reason, SMILE consultations were slightly different from the other three trials from the outset. Recruiters had an in-depth understanding of trial concepts and appeared more comfortable discussing uncertainty with families:

> *Recruiter S2:…The main thing to go on to is the concept of the design of the study, in health research we do randomised controlled trials… usually there's two different treatments being looked at…you need to feel happy about being in either group, [brief explanation of both treatment groups] and the reason we're doing this whole study is because we don't know which treatment works and whether one treatment might be better than another. We didn't want to leave the people in the Lightning Process group without any medical backup, so we didn't feel it would be ethical to do that, so that's why the medical care is still in there…*
>
> *Recruitment consultation:SMILE Specialist Medical Care 15yrs Female*

In early SMILE consultations many families explicitly expressed a preference for the specialist medical care plus Lightning Process trial group (see: Section 5.3.1 How and when preferences are expressed). Recruiter 'acceptance' of preference often involved missed opportunities to explore and challenge preferences. Instead recruiters responded by consistently stressing the need for "*two groups*" and sometimes highlighted trial rationale. The recruiter reassured the mother, *"that's fine if you feel that way"* but in early consultations recruiters did not provide balancing information about the specialist medical care group of the trial or discuss preference any further, instead it was accepted that the family would *"take pot luck":*

> *Mum S4:…I'm happy to go ahead, I must admit I would prefer, I think, to be in the trial group for the Lightning Process but equally I'm just happy that now we've seen the service and we are getting some positive treatment and we've had a lot of feedback from them already and a lot of steps forward already so I'm feeling very positive about that, if nothing was happening there I'd be feeling a bit desperate, so no, I'm fine with that and whichever way we go…*
>
> *Recruiter S2:…Okay, yeah, I mean, I do labour the point about the two groups being very important to us… Because if you felt at this point that you couldn't, you wouldn't be bothered to carry on with the study if you weren't in the Lightning group, then umm*
>
> *Mum S4:…I can see that being an issue*
>
> *Recruiter S2:…But that's fine if you feel that way, but I'd say, then let's not go any further, if you feel, in the way that you've just described, that you're willing to take the, pot luck, and you'll carry on…*
>
> *Recruitment consultation:SMILE Specialist Medical Care 12yrs Male*

After feedback was provided by qualitative researchers (NM and LB) the recruiter also more consistently discussed the possibility that the Lightning Process "*may not add anything*" and that those having Specialist Medical Care may get better "*just as quickly*":

> *Recruiter S2:…We don't know, the state of knowledge we're at is that we don't know whether it [Lightning Process] does add anything or not, and this is why, when they've started doing the clinical management, [Specialist Medical Care] with the clinical team, we could find that people get better just as quickly on that rather than having them both together.*
>
> *Recruitment consultation:SMILE Specialist Medical Care 17yrs Female*

When recruiters didn't explore preferences for treatment during the course of the recruitment consultation, they were often expressed for the first time immediately after randomisation. Although recruiters tried to explore preference, some families appeared reluctant to disclose their views. Families either underestimated or concealed the extent of their preference for treatment. If families were randomised to their non-preferred group there was disappointment or elation depending on whether or not they were allocated their preferred treatment. The trial context is perhaps important when considering non-disclosed preference, because similar treatment was not easily available for these families outside the trials (SMILE and FITNET-NHS). The examples below are taken from two families, showing their feelings and preferences before and after randomisation:

> *Mum S33:…If [patient name] gets it, [Lightning Process] it's a bonus, she may not get it anyway, in which case she'll just have what's available currently, [specialist medical care]*

Recruitment consultation:SMILE Specialist Medical Care 15yrs Female

Mum S33:…[patient name] put on a face…'yes I'm fine, yes I don't mind' and I remember thinking at the time, you know, it's all very well to put an adult through the disappointment of not getting that, there's another thing to put a teenager through that, I do remember feeling very uncomfortable with that whole, the way that it happened, there and then… I don't think it's very fair on them, certainly as a mum I can't even begin to tell you the disappointment that you feel, that you think I'm just going to be the comparison group and that's it, and to me there's no benefit in that…

Interview:SMILE Specialist Medical Care 15yrs Female

[Participant not interviewed; family paid for their child to complete the Lightning Process.]

Recruiter F1:…Dad, have you got any thoughts about either of the treatments?

Dad F2:…We'll spin the wheel and see what happens.

Recruitment consultation:FITNET-NHS Online CBT 13yrs Female

[Discussion before randomisation.]

Recruiter F1:…and you've been allocated to the FITNET study, the FITNET treatment

Dad F2:… heeeey! [cheers, laughs] I had a slight preference for that one.

Recruitment consultation:FITNET-NHS Online CBT 13yrs Female

[Discussion after randomisation.]

Exploring preference

The SMILE trial was similar to FITNET-NHS in that many families could not access the Lightning Process (one treatment group) outside of the RCT. Although recruiters explored preferences from the beginning of the RCT, there were still instances when recruiters missed opportunities to promote a position of equipoise. Recruiters did not always highlight that the Lightning Process may not be necessary to facilitate recovery when parents and young people expressed a preference for the specialist medical care plus Lightning Process group of the trial.

Early consultations in both FITNET-NHS and SMILE trials generally involved gaining confirmation from the family that they understood and were willing to accept randomisation to select treatment. In addition, the recruiter in SMILE also explored whether the family *"wouldn't be bothered to carry on"* if they were randomised to their non-preferred treatment. This was not apparent in FITNET-NHS, and recruiters lack of preference exploration may have been related to an underlying assumption that families were happy to take part in the trial because they did not have local service provision. Examples of acceptance of preference and missed opportunities were used for training and feedback during each of the four trials (see: Acceptance of preference and missed opportunities to explore preference).

Recruitment training had been carried out prior to opening both the MAGENTA and CONTRACT trials to recruitment (see: Figures 5:4 and 5:6: The impact of communication training on recruitment figures). Recruiters were aware that preferences for treatment would be apparent, and that it was acceptable to gently

explore these preferences by offering balanced information about both treatment groups, and at times this was apparent in early consultations. But instead of challenging preference, recruiters more often gently explored families' reasons for preference, and then accepted them without providing balancing information about the potential 'risks' of surgery and information relating to the rationale of the trial:

> *Mum CF1:…Alright, I understand it and when my husband comes...I'll just discuss with him...*
>
> *Recruiter CF14:...Fine...I, I'll leave you to convince him.*
>
> *Recruitment consultation:CONTRACT Antibiotics 4yrs Female*

It should also be noted that CONTRACT recruiters did not try to balance preference for treatment when families expressed preference for antibiotic treatment, this was generally accepted as a willingness to enter the study since antibiotic treatment was not routinely available outside the trial. There was one instance of balancing preference in the opposite direction, by pointing out the benefit of surgery when a family showed a very strong preference for antibiotic treatment. This family withdrew from the trial when they were randomised to the appendectomy group:

> *Recruiter CD9:…He's quite unusual because he's got very, potentially very early appendicitis, the scan only showed some mild inflammation. So, um, you know, we've talked about the fact that we would potentially, um, just give him antibiotics for now and see how things go… So, are you saying that if you went into the study and the computer said, appendicectomy, you would immediately drop out? Is that right?*
>
> *Mum CD14:…Yes.*
>
> *Recruiter CD9:…If we treat him with antibiotics now there is still the possibility it could come back again. So, you know, we know that doing an*

operation definitively treats it. So, yeah, it does have to be either or... But you can change your mind.

Recruitment consultation:CONTRACT Appendectomy 8yrs Male

[Withdrew from trial.]

Some of those recruiting to the CONTRACT RCT felt at times that preference exploration might feel coercive for families:

Recruiter CD21:…What I didn't want to do was to be the person who pushes it too much and they, and they complain. So, I try to be as, as objective as possible. Some said yes, some said no, and that was it.

Recruiter CE14:…Dad's body language, just the whole sort of thing was, you know, I mean I didn't feel I was gonna push it necessarily, which I guess I could have done even more but it was sort of clear to me that they weren't gonna agree.

In contrast, several families from all recruiting sites discussed during interview that they did not feel pressurised to participate in the trial:

Mum CF15:…We were told it was completely our choice, there was no pressure.

Interview:CONTRACT Declined trial 5yrs Male

Mum CE7:…There was no pressure was there?

Young Person CE7:…Yeah, there wasn't a lot of pressure and, um, yeah, it was a very kind of, er, not quite...

Mum ME7:…Quite inclusive but it wasn't, instructive and you weren't made to feel guilty.

Young Person CE7:….Actually, I think the most important thing which, was the amount of information that they could give you and tell you all about the trial, um, which gives you kind of the knowledge to then make your decision.

Interview:CONTRACT Antibiotics 14yrs Male

Mum CD8:…Yeah, I didn't feel rushed or pressured to make a decision or, pressure to take part. I thought that all the information was given in quite an unbiased manner...and it was all very clear.

Interview:CONTRACT Declined trial 13yrs Male

During CFS/ME trials recruiters and health professionals did not discuss coercion as an issue when exploring preference, but they did emphasise the importance of 'patient choice' and the way in which trial participation might limit patient and family choice, because families had preferences for a particular intervention:

Health Professional ME:…Some of them sense that it's a bit more restrictive, [trial involvement] i.e. you know you have no choice. They might say oh well I want to do Graded Exercise Therapy but most of them understand the randomisation

Health Professional MB:…I think it's also about choice and I think that when you are asking people to go on a journey, which you know, without sounding a bit glib calling it a journey, but when you ask people to go on a journey I believe that most people are more motivated to – to actively

engage in that journey if they feel they have some element of control and choice.

Health Professional MS:…I really emphasise the consent issues that it is their choice to engage with this or not and they can change their mind at any time so that they should not feel under any obligation. I really heavily stress that because I don't want people to feel at all pressured that they are not going to get a service unless they enter the trial and I say to them "It is absolutely your choice" and that's part of my preamble you know just in terms of speaking to people about research.

5.3.4 Health professional and recruiter equipoise

This section reports themes and findings relating to the way in which recruiter and health professional equipoise influenced discussions of trial treatments with families. Interviews were not conducted with members of the Specialist CFS/ME team during the SMILE RCT, therefore these themes were developed from interviews with health professionals who were recruiting to or caring for patients following treatment pathways in the MAGENTA, FITNET-NHS and CONTRACT trials.

Individual versus collective equipoise

During interviews several health professionals reported a lack of individual equipoise in relation to their own personal views about the treatment pathways offered in the each of the trials. Other interviewees stated that they knew colleagues who did not have individual equipoise, but collectively "*the team*" had all agreed to *"be in it"*:

Recruiter CF2:…Because we… all agreed and the team [agreed] to be in it, to be all in it. There are people who don't necessarily agree with is it worth it, and is it okay to do it, and all those questions.

During the MAGENTA trial lack of equipoise centred around not being able to introduce 'prohibited' elements of activity management. There was an assumption that outside the trial most patients would be treated using activity management techniques, which was a 'standard' less restrictive and more familiar approach:

Health Professional FU:…If people don't agree to MAGENTA then we do activity management...

Health Professional MP:…I think it feels like the activity management has more content but only because that's what I'm used to doing. It feels like maybe I'm a bit too restrictive when I'm doing Graded Exercise Therapy because I'm so aware of not saying anything cognitively-based.

Health Professional MA:…Sometimes after my assessment I can tell which would be better for them so I have to keep 'stuhm' about that…it's very difficult if they're given Graded Exercise Therapy knowing that activity management will help them, that's very, very difficult.

There were also suggestions that outside the 'trial' setting, (MAGENTA and FITNET-NHS) health professionals used a mix of activity management and Graded Exercise Therapy which was a 'preferred' way of working:

Health professional MQ:…Our general treatment there is a sort of a smorgasbord approach where you can have a bit of exercise through it. You can have a bit of that and throw in a bit of CBT and whatever. And some of them [families] quite like that. I suspect many of the therapy team quite like the smorgasbord approach as well…because you obviously don't know how people are going to respond to particular treatment until they've tried it.

Rationale for the MAGENTA trial (focussing on a one treatment approach, see: Section 2.5.2) was discussed by only one member of the specialist CFS/ME team, in contrast to the more widely held team opinion that a mixture of the two treatment approaches was more beneficial for young people:

Health Professional FK:…It is an awful lot of information to have altogether, [activity management and Graded Exercise Therapy] because it is every part of your life really.

Graded Exercise Therapy was never discussed as a stand-alone treatment for CFS/ME outside the MAGENTA trial, and was always viewed as an additional 'tool':

Health Professional FK:…So that's the reason, sort of trying to split those two [activity management and Graded Exercise Therapy] was quite an issue to begin with because it was so different to what you've been doing… So there was a lot of concerns about 'oh well am I giving the person the best'. You know shouldn't they have activity management as opposed to that.

There was also an awareness of online ‘activists’ influencing families’ decisions to participate in the MAGENTA trial, because of a negative campaign suggesting Graded Exercise Therapy was dangerous for those with CFS/ME:

> *Health Professional FO:…My last few where they have turned down MAGENTA is because they wanted activity management, but that may be biased by the fact that the activists have been adversely affecting the impression of Graded Exercise Therapy.*

Team views in relation to the two treatments used in the FITNET-NHS trial became less polarised as the trial progressed:

> *Recruiter F1:…Initially we thought that the two groups were quite different. But I think they're more even than I realised in their treatment of CFS.*

> *Health Professional FR:…But I might be biased ‘cause I’m doing the activity [management] [laughs]… I’ve definitely had preferences in MAGENTA but not really in FITNET.*

Many surgeons recruiting to the CONTRACT trial minimised the risk of surgery and anaesthesia. However, only a minority of surgeons reported a strong preference or ‘bias’ for surgical treatment for appendicitis:

> *Surgeon CE12:…Very rarely have I regretted operating… There have been several times in my career where I think, do you know, I should have done that earlier… I’m honestly not trying to make a case against the antibiotic arm at all, but I am confessing my personal bias.*

Most surgeons recognised that culturally, in the UK appendectomy is viewed as the standard and traditional approach to treat appendicitis which posed a challenge when introducing the trial to families:

> *Recruiter CD20:…They [families] see surgery as the answer and not antibiotics, they don't see [antibiotics] as the answer because culturally [surgery] that's what was always done… So they're quite frightened to think that you're not… they think they've got some sort of ticking time bomb inside them, and it might burst and then terrible things are gonna happen… and I think sort of explaining that stuff to them is quite complicated and new.*

Some surgeons were surprised that families wanted 'an alternative' treatment for appendicitis:

> *Surgeon CF5:…The most surprising thing was that there are families who are looking for an alternative treatment other than surgery.*

At the same time recruiters reported that there was 'collective' equipoise for the CONTRACT trial. Collectively each of the three recruiting teams felt that there was a question to be asked about the acceptability of antibiotic treatment for appendicitis, and the need for well conducted RCT research with a paediatric population. Some health professionals delivering RCT treatment on the wider CFS/ME team also reported commitment to the FITNET-NHS trial:

> *Recruiter CF10:…I do really like it [the trial] and I really hope that it does well and that it continues after this [internal-pilot] phase.*

Health Professional FT:…No, as I said, I'm really excited. I'm really committed to it as a trial and I just think it's gonna be interesting to see what the results are.

One surgeon presented antibiotic treatment as a "natural progression" in medicine, just as techniques change and improve, so do treatment methods:

Surgeon CE18:…I found that it's quite useful to say that we have changed the way we operate on appendicitis, or we've gone from an open appendicectomy to a laparoscopic appendicectomy and we now have an extra level of that, but we are comparing the two different treatments… I don't call it conservative, I don't call it anything. I call it antibiotic process, antibiotic treatment versus surgical treatment.

Discussing uncertainty and equipoise: what would you do?

In clinical practice health professionals may be used to reassuring families with their medical knowledge, thus reducing uncertainty in relation to treatment efficacy and outcome *"you're the expert"*. In contrast, in a trial environment there is more emphasis on uncertainty, explaining why 'randomisation' is used, because of a lack of evidence-base can be problematic for health professionals:

Health Professional ME:…I think it's interesting that when you talk about research… in effect you're admitting to patients and families at the very outset that there are still things that we don't have answers to and we don't know what the effective treatments are.

Health Professional MB:…Patients are coming to us for specialist advice. They are not, you know, 'Well you choose. Which one would you rather

do? Well what do you think [own name]? You're the expert' you know, or 'You're the one who supposed to know the answer to that question. We don't know, you know, we don't know what we're doing, whether we're going left or right. You must know what comes if you turn left, if you go left or right or whatever'…

Some recruiters highlighted that despite uncertainty, a lack of evidence-base and the collective equipoise of the wider team, during the early stages of recruitment they found conveying equipoise problematic, potentially because they did not have personal equipoise at that point in time:

Recruiter CE18… I was a little bit sceptical about it [the trial] because, you know, you always come in and think, okay, what would I say, you know, if someone came to me and said, okay, well, let's give your kid antibiotics, I would say, well I don't think so, I want the appendix out… So the first patient I contacted, it didn't work out, and I didn't even record the conversation which was a bit bad really, but it was quite clear that I didn't go in full-heartedly and I didn't convince the parents because I wasn't convinced myself.

At times parents asked recruiters, (and health professionals on wider clinical teams) what they would do, as a parent, if they were in their situation, or in terms of their professional experience. Some recruiters appeared to struggle with the uncertainty of using randomisation to allocate treatment and did not draw on trial rationale or state a position of personal or collective equipoise in response parents' questions:

Mum M103:..What would you advise her to do, not even thinking about all the study and stuff like that, what would you think would be the best idea?

Recruiter 1:…I have literally only got the little pink piece of paper, with your address and your phone number, [laughs] I think if you feel, you obviously know yourself very well [patient name]… and you know [patient name] better… [mum's name] if you feel, that she would particularly benefit from one or the other, and feel very strongly… then it's probably better not to be in the study

Recruitment consultation:MAGENTA activity management 15yrs Female

Dad CE13:…What would you do?

Recruiter CE8:…What would I do, really difficult question. Me personally, I mean, it's really awkward, isn't it? I can't really answer that question. I mean I, I would always, the thing I would say about participating in a research study regardless of which arm you go into is that you're monitored really closely.

Recruitment consultation:CONTRACT Antibiotics 5yrs Male

[Treatment failure - revert to surgery.]

Health Professional MA:…They quite often say to me, what would be best for me, umm, and I say well I can't answer that, because that will mess up the results and make you bias. But that has come up quite a bit. 'What if I get the activity management and I want Graded Exercise Therapy?'

Five recruiters and one research nurse discussed whether they would consent to their child's involvement in the CONTRACT trial, (during recruitment consultations and/or at interview) all but one recruiter stated they would. Only one recruiter responded to this question from a position of equipoise during a recruitment

consultation, highlighting that there was uncertainty *"we don't know what's the right thing to do"*:

Dad CD21:…So being a surgeon and mother, what would you do then?

Recruiter CD9:…Good question. Erm, I think it's really important that we answer these questions, you know, because we don't know what's the right thing to do…I'm a believer in research and I think that, you know, the more people we have in the study, the better it is.

Recruitment consultation:CONTRACT Antibiotics 5yrs Male

[Withdrew from antibiotics as felt child was getting worse.]

Research nurse CE1:…Having two young kids myself I did wonder would I take part in the study, it's always one of the first things that, would I do that with my children? Erm, and yes, I probably would.

Recruiter CE7:…So I think it's always a very good test for a trial if you, if you're on the battle line thinking, if it was my child I'm not sure I'd be up for this but, you know, I genuinely think I would be.

Questioning the eligibility criteria

Those perceived to be at the extreme end of the trial eligibility criteria (severely affected) were problematic for those recruiting to the CONTRACT trial. In these cases perforation was 'suspected' but not clearly confirmed, *"the only way to know for sure was to operate" [Recruiter CE7]*. Some families were considered eligible for the trial and others were excluded due to 'suspected' perforation:

Recruiter CD5:…Cause, here's a one of the other challenges… one of the other things I find difficult for some patients is picking the ones who are simple and not perforated, and there are at least one or two where we've not judged it quite right. In retrospect, at the time it felt like the right decision, but in retrospect we haven't…

Recruiter CE7:…So that's something I think we would try and redefine or define better. [eligibility criteria] I think there was always a tendency to slightly – especially early on, I want to say well I think they might perforated, we won't bother, rather than...I think the default early on was more, it's extra work so let's be cautious and let's not put them in…

One patient was discussed as 'mildly affected' and this was challenging because these patients would 'routinely' undergo surgery outside the trial, and in this instance the family had a preference for antibiotic treatment (Consent to trial despite preference for treatment):

Recruiter CD9:…Yeah. Well I was, he's, like I said to you, he, he does show signs of appendicitis. He's not completely fine… I think this is a difficult situation, because it's not straightforward. [Child was not severely affected].

Those introducing the MAGENTA RCT sometimes decided not to introduce the RCT because of 'softer' eligibility issues, or less severe co-morbid conditions that didn't meet the exclusion criteria:

Health Professional MO:…If you looked at it on paper you'd probably say she is eligible but actually taking all those sort of softer things into account, I just couldn't, you know, I just – I just couldn't do the transition

over into saying "Let's do the – let's do the…" you know, it was hard enough doing the consultation without adding that on to the mix really…

Health Professional ME:…My only real issue in some of it, is that the research criteria is quite restrictive…a lot of them do have a lot of high anxiety, and you can't… I can't often at an initial consultation know how much is Chronic Fatigue….and people who have multiple other stuff, um I know we probably should be recruiting them but you know someone has Asperger's chaotic lifestyle all over the place, whatever and I think "Oh."

In one case, the eligibility of a young person who had already been recruited was questioned by a treating colleague going forward:

Recruiter F10:…She got the activity management arm and then the clinician who picked her up after the first Skype session… stated I don't think she is appropriate for research because she's so severe this isn't right. Ah like should I not have recruited her but then there's no... The exclusion criteria don't mention severity in any way.

Discontinued treatment, treatment failure and recurrence

Cases of 'treatment failure' in the CONTRACT trial, when antibiotics either failed to improve symptoms during the inpatient stay, or when young people were discharged because they had shown improvement but experienced a 'recurrence' of symptoms and were re-admitted to hospital, were discussed as problematic by health professionals at interview:

Recruiter CF8:…I felt really upset. Um, I felt, I felt a little guilty that I'd recruited them to the trial and then it [antibiotic-treatment] had failed and

they actually ended up having a whole second hospital admission with prolonged antibiotics. And then having to come back again for the operation that he didn't want in the first place.

Some treatment failure was not perceived to be 'true' failure but more patient or parent choice to opt for surgery:

Recruiter CD5:…I think if you get the right patient, if you get the nice and simple ones. The ones that we've had fail, I've looked into those quite closely, because we had five fail and it felt like a lot… the first one was the boy that I mentioned earlier, who probably just was getting bored of sitting there on antibiotics and was wanting something exciting like an operation. Did it really fail in him? No, I don't think it did...

There was also a perception that cases of treatment failure had a negative effect on the motivation and confidence of the wider team:

Recruiter CF11:…I had one of my consultant colleagues who was initially happy to, um, recruit his patients into the study, he was the one who saw this patient after, [treatment failure] so he's not wanting to be involved now…So that certainly has affected his equipoise. And I think, you know, some of the registrars I imagine might feel the same way.

Research nurse CF10:…They [ward nurses] hate it. [the CONTRACT trial] she's like, 'oh, God', sort of, you know, that sort of reaction… it doesn't work, it doesn't work, you know. That's what she said. … really surprised me because that was the first reaction I received like that and, to be fair, not many of our patients had to change treatment… Perhaps they remembered, the last boy that…he had to go into theatre because he got quite poorly and obviously the antibiotics weren't enough.

An early case of treatment failure at one site was highlighted as affecting team equipoise. This site did not record any recruitment consultations or recruit any eligible participants for three months after this case, despite five patients being screened as eligible for the trial:

> *Recruiter CF8:...Failing it that has put people [on the team] off actually….It was a bit of a disaster…It's affecting people's, what is it, equity.*
>
> *Researcher 2: …Equipoise.*
>
> *Recruiter CF8:…Equipoise…definitely.*

One family in the MAGENTA trial felt their treating health professional had facilitated the decision to cross-over to the opposite treatment group:

> *Young person M29:…Well I suppose I was very eager to sort of start doing a bit more exercise 'cause we completely cut out [exercise] on the activity management…they [health professional] advised that we go on to the other one because that actually enabled me to do some. So that's how we got on to it [Graded Exercise Therapy].*
>
> *Interview:MAGENTA activity management 15yrs Male*

> *Health Professional MQ:…I think I had one young person who started to indicate quite strongly that… after a few months that they were wanting some guidance around the physical exercise and some GET guidance… I did talk to them, about the choice… went through the options with them and they chose to withdraw and to have the GET guidance. So black mark against my name [laughs] probably.*

5.4 The impact of treatment preference on recruitment and retention in four paediatric RCTs

5.4.1 Recruitment: Preference and reasons for trial decline

A full breakdown of all recruitment figures and CONSORT diagrams for each trial can be found in the Appendix 7. Preference for treatment was the main reason provided when families declined participation in three of the four paediatric RCTs (MAGENTA, FITNET-NHS and CONTRACT).

Eligible young people (families) declining the four trials because of preferences for treatment ranged from 4-27%. Those declining due to preference, as a percentage of the overall number declining ranged from 15-60%, with the greatest number declining because of preference for surgical treatment in the CONTRACT feasibility RCT. The number of eligible families declining each RCT because of preference are displayed in Table 5:10, along with the time point at which families declined (e.g. initial eligibility assessment, or after the recruitment consultation). Reasons for decline were recorded by the health professionals on the wider clinical teams, or recruiters who assessed patients for eligibility. Fourteen families who declined participation went on to take part in interviews during the MAGENTA and CONTRACT trials (Appendix 9 for characteristics of participants how took part in interviews).

Table 5:10 Eligible families declining four paediatric RCTs due to preference

Trial	Total eligible young people	Total eligible young people declined: All reasons N (%)	Total eligible young people declined: Preference N (%)	Total declined by time point: Preference N	Time point of decline	Reason for decline (preference)	Breakdown declined by reason
SMILE	310	49 (16%)	12 (4%) (15% of those who declined)	3	First clinical assessment	No to group work	2
						Child wants to do Lightning Process	1
		33 (11%)		9	When recruiter made contact	No to group work	4
						Mum interested in Lightning Process but child did not want to do the course	2
						Child wants specialist medical care	1
						Lightning Process would impact Specialist Medical Care	1
						Child wants to do Lightning Process	1
MAGENTA	161	23 (14%)	27 (17%) (33% of those who declined)	6	First clinical assessment	Preference for treatment / didn't like the idea of randomisation	6
		58 (36%)		21	When recruiter made contact	Would like Graded Exercise Therapy	3
						Unwilling to use Graded Exercise Therapy	9
						Would like Activity Management	5
						Unwilling to use Activity Management	2
						Would like both: Graded Exercise Therapy & Activity Management	2
FITNET-NHS	148	11 (7%)	28 (19%) (58% of those who declined)	7	Referral	Preference for face-to-face appointment	7
		24 (16%)		13	First phone call	Preference for face-to-face appointment	10
						Unwilling to use Skype	2
						Unwilling to use online treatment	1
		13 (9%)		8	Eligibility assessment	Preference for face-to-face appointment	7
						Unwilling to use Skype	1
CONTRACT	131	58 (44%)	35 (27%) (60% of those who declined)	35	When recruiter made contact	Preference for surgery	35

SMILE

Twelve eligible young people declining the trial because of a stated preference for treatment (4%). The main reason for refusal during the SMILE trial was ‘not interested’ at the end of the initial assessment appointment, (n = 35, 71% of those who declined at the end of the initial assessment). ‘Too much at the moment’ was provided as a reason by eight families (16%), who had provided consent to contact details but declined when recruiters made contact. It was not possible to establish whether these young people (or their parents) were ‘not interested’ because they had a preference for treatment outside of the trial i.e., for Specialist Medical Care, or they did not wish to participate in the Lightning Process course because they felt that was ‘too much’. Alternatively, they may not have been interested in participating in research more generally. These reasons were provided by families but there may also have been some degree of ‘interpretation’ by health professionals or recruiters on the SMILE research team.

One-hundred and twenty-five (48%) of the consent to contact forms given out to young people at the initial clinical appointment were not returned, (via post or at the next follow-up appointment) so the research team could not make contact with these families. It was not possible to establish why these young people (or their parents) did not wish to engage with the RCT, and potentially some of them may have had preferences for treatment. The number of young people who returned consent to contact forms but declined due to preference when the research team contacted them was nine (27%). When contact was made by the research team more varied and detailed reasons for trial decline were recorded than those detailed by the clinical team, and the most frequently recorded reason for refusal was ‘preference for

treatment'. Data obtained from recordings of first clinical assessment as part of the SMILE RCT (not presented in this thesis) suggested that some health professionals felt it was too burdensome for young people to complete the consent to contact forms at the end of the initial clinical appointment because of their chronic fatigue symptoms.

MAGENTA

Twenty-seven eligible young people declining the MAGENTA trial because of a stated preference for treatment (17%). To ensure as many families as possible received information about MAGENTA, the health professional who conducted the initial clinical appointment gave the family a brief verbal introduction to the trial and sought consent for further contact, (a recruitment consultation). Only 23 families declined further contact (14%). Nearly half of families who declined the MAGENTA trial at the end of the initial assessment appointment were recorded as 'reason unknown', (n = 11, 48%). In contrast, only three families who declined when the research team made contact (5%) were recorded as 'reason unknown'.

FITNET-NHS

Twenty-eight eligible young people declining the trial because of a stated preference for treatment (19%). Preference for a face-to-face appointment with the specialist CFS/ME service outside the RCT was the most common reason for families declining to participate in the FITNET-NHS trial at all time points (referral, first phone call and eligibility assessment). Families could 'request' a face-to-face appointment, (or this could be offered by the clinical team) but it was dependent upon obtaining

funding from the families local NHS trust, and their ability/willingness to travel long distances to an appointment. Three did not want skype appointments and one parent was not comfortable using online treatment. Neither of these treatment approaches (skype appointments with the specialist service or online FITNET-NHS modules) were available to patients outside of the trial.

CONTRACT

Thirty-five eligible young people/parents declined the CONTRACT trial because of a stated preference for treatment (27%). Only three reason codes were used to categorise all 58 declining families (see: CONSORT diagram Appendix 7) and preference was the main reason reported for trial refusal (by 60% of those who declined). After nine months of recruitment I analysed whether the rate of families declining participation was similar across CONTRACT sites, or whether families in one site were consistently declining more, and/or for a specific reason e.g., 'surgical treatment preference'. The rates of decline were similar across sites when analysed against the percentage of families approached. However, site D consistently used the reason, 'preference for surgery' more than sites E & F, where conversely the reason 'did not want to take part in research' was more frequently used (see: Appendix 8, CONTRACT: Reasons for decline by site at nine months) All families were approached shortly after a diagnosis of acute appendicitis had been made by a treating surgeon. Informed consent and randomisation happened within four hours of the recruitment consultation. A reason was provided/assigned for all families who did not provide consent for their child's involvement in the trial.

Consent to trial despite preference for treatment

There were instances where families consented to trial involvement, despite discussing preference during the recruitment consultation. This was apparent in the SMILE and MAGENTA trials, although during the SMILE trial many families expressed these preferences more overtly after randomisation, when they were given the allocated trial group (see: Section 5.3.1: How and when preferences are expressed). Analysis of recruitment consultations from the MAGENTA trial suggested parents or young people felt 'reassured' about their non-preferred treatment before randomisation, when recruiters explored preference (e.g. *"Do you understand the difference between the two groups?"*). Recruiters reassured families that the graded exercise pathway did not demand high levels of exercise, *"with Graded Exercise Therapy people have been a bit concerned with the word exercise… it's the name of the treatment rather than a description of what it actually is"* (see: Section 5.3.3: Understanding how recruiters' responded to preference). However, interview data suggested some families still had some reservations about their non-preferred treatment group despite having consented to the trial:

> *Mum M72:…Okay, that's the thing that worries me, because at the moment he doesn't get any exercise…I was scared it was going to get him moving too much… Worth going for it, we've got nothing to lose, and it's helping others.*
>
> *Recruitment consultation:MAGENTA activity management 10yrs Male*

> *Mum M72:…I would have been a bit scared about what he would've been made to do [in GET group] because I don't know what he would've been made to do… I'm sure it would have been tailored more specifically so in hindsight I think yeah it probably would've been okay but at the time when*

I was asked I thought 'Oh god I hope we get the you know the activity management one rather than the exercise one' because I was a bit 'aaahhhh'.

Interview: MAGENTA activity management 10yrs Male

During recruitment to MAGENTA it was apparent that families valued the opportunity to help others in the future (see: 5.3.2 Reasons for preference – Altruism). Both treatments were available outside the RCT but families still wanted to participate in the trial despite their preferences for treatment:

Mum M23:…I knew which one I wanted him to go on, if that makes sense. And we were just lucky and he was randomised on that one anyway… With leukaemia treatment everybody's on a trial… and those trials benefit people who are getting treatment years and years down the road.... I think research studies are worth their weight in gold.

Interview: MAGENTA activity management 12yrs Male

[Only mum interviewed.]

In contrast, families eligible for FITNET-NHS could not access either treatment outside the trial without travelling long distances for face-to-face appointments. Fewer FITNET-NHS families expressed strong preferences for treatment before randomisation, and when preferences were discussed the family usually followed with a discussion about the fact that they would be happy to accept either treatment group because they wanted specialist advice. Families were more open about their preferred treatment after randomisation or when interviewed:

Mum F1:…Well I'm very pro CBT because, I mean I'm a counsellor anyway….obviously we are open to trying both, because, both could help…I mean when I first heard of it, in fairness my thoughts were, hopefully we will get into the CBT part because I think that could be really helpful… but if we don't, we don't. We will, [patient name] will give it a go.

Recruitment consultation:FITNET-NHS Skype activity management 14yrs Male

It seems possible that preference for a particular intervention arm might affect participant (and parent) engagement with a trial as well as the intervention itself (particularly when it is a behavioural intervention). For example, a family randomised to the Specialist Medical Care plus Lightning Process group who decided not to attend the Lightning Process course, (and later withdrew from the trial) did not express preferences during the recruitment consultation but did so at interview post randomisation. This family did not return any outcome measures during the RCT. Also, the family raised some concerns about the group work involved in the Lightning Process course during the recruitment consultation:

Recruitment consultation SMILE:

Mum S5:…[Patient name] did have one concern, group work and whether I could go, but [you] answered that, I'd be able to go with her and she's a lot more happy about that aren't you [all laugh]

Recruiter S2:…I guess from the lack of questions you're happy to go onto the next stage?

Mum S5:…Definitely, yeah.

Specialist Medical Care plus Lightning Process 13yrs Female

Interview after randomisation SMILE:

Mum S5:…We were tending to think…perhaps just the consultant care [Specialist Medical Care] Cos umm, going through the pack [PIL] it is quite overwhelming, quite intense… but obviously having someone talk through it… she was a bit worried about going into groups and things at the course but when [recruiter] said I could come [patient name] was quite happy.

Specialist Medical Care plus Lightning Process 13yrs Female

[Participant did not attend Lightning Process course and withdrew from trial.]

One family from the CONTRACT trial withdrew consent immediately after randomisation because they wanted antibiotic treatment and their child was randomised to the surgical group. These parents had expressed a strong preference for antibiotic treatment before randomisation because they were told their son had *"potentially very early appendicitis"* but they were informed they could, *"change their mind at any point" [Recruiter CD9]* presumably because antibiotics were not routinely available outside the RCT. The point at which this family made their decision to participate was not audio-recorded (see: Sections 5.3.1 Missing conversations from the consultation process, and 5.3.4 Questioning the eligibility criteria):

Mum CD14:…The only question that I've got is, if he does get chosen, [for surgical group] can we decline the operation at this point?

Recruiter CD9:…So what happens when you go into the study is you kind of have to be happy to go with either option. You have to be happy to go with the surgery or antibiotics. Um, but if you… you can change your mind. So, if you're in the study, you can change your mind at any point.

Mum CD14:...Right, okay. So if I say yeah now, and then I could change my mind. I'm just worried, like I said before, of putting him through an operation that he doesn't really need.

Recruitment consultation: CONTRACT Appendectomy 8yrs Male

[Withdrew from trial.]

The impact of communication training on recruitment figures

Training sessions that focused on best practice and included strategies to communicate equipoise and explore treatment preferences, were routinely conducted in the MAGENTA, FITNET-NHS and CONTRACT RCTs. Training and recruitment figures were not formally conducted or monitored during the SMILE trial. (see: Section 3.4.7). During the MAGENTA RCT, four training sessions were provided in months -1, 2, 6 and 12. Each session was associated with an increase in the percentage of eligible young people recruited the RCT. During month 11 of the MAGENTA trial the specialist paediatric CFS/ME service moved to a new site and recruitment decreased significantly during month 12.

= Communication training

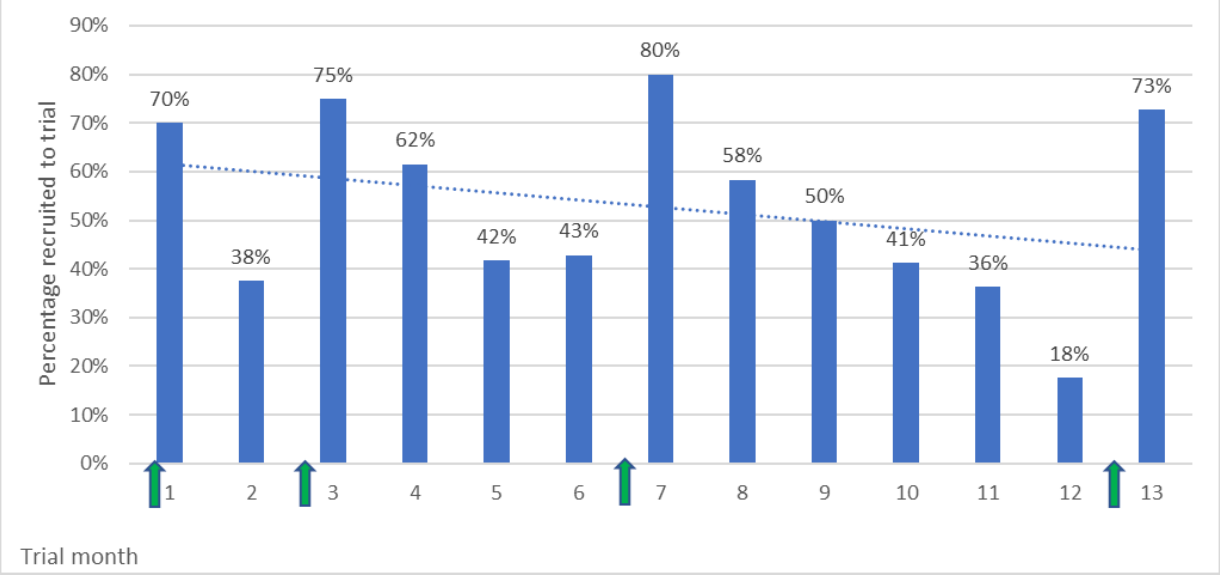


Figure 5:4 Training MAGENTA feasibility: Percentage recruited of those eligible [Sites 1 & 2]

Figures 5:5 and 5:6 show overall increases in recruitment as the FITNET-NHS and CONTRACT trials progressed:

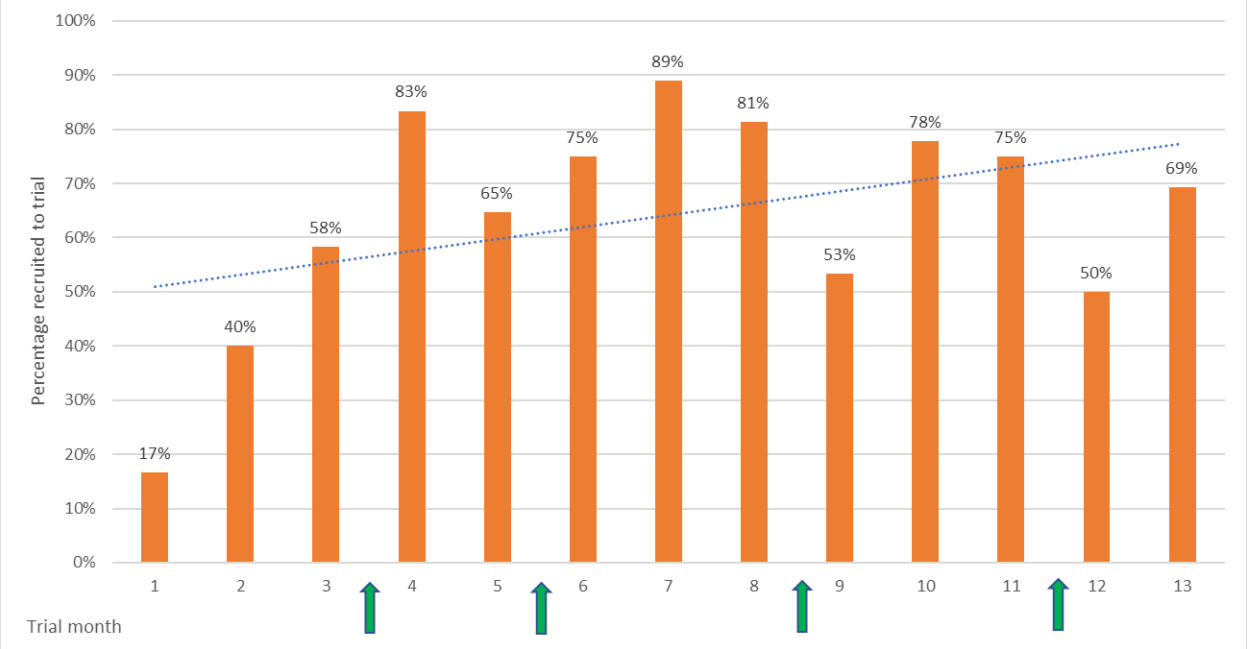


Figure 5:5 Training FITNET-NHS Internal pilot: Percentage recruited of those eligible for the trial by month

= Communication training

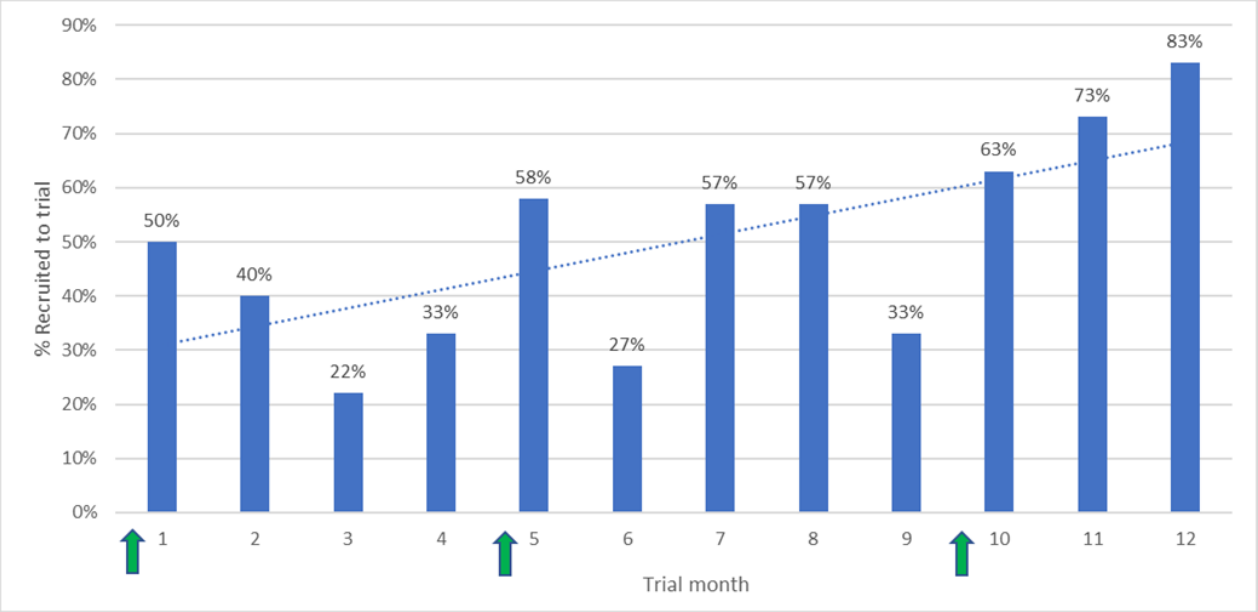


Figure 5:6 Training CONTRACT feasibility: Percentage recruited of those eligible [sites D, E & F]

Preference for treatment had a negative impact on recruitment, it was the main reason provided when families declined participation in three of the four paediatric RCTs (MAGENTA, FITNET-NHS and CONTRACT). When a trial was introduced, and participation declined, health professionals treating CFS/ME were reluctant to ask families if they were willing to provide a reason for their decline. This reluctance may have been compounded by the condition under investigation (CFS/ME), or the time at which information was provided (at the end of the first clinical appointment) and associated worries about burden. Those recruiting to the FITNET-NHS trial were more willing to explore reasons for trial decline with families via telephone during discussions about patient eligibility.

The way in which 'reasons codes' for declining patients were used and recorded did not appear to be consistent across recruiting sites (CONTRACT RCT) or at different time points in the recruitment process e.g. consent to contact and consent to trial (SMILE and MAGENTA RCTs). More general reason codes such as 'not interested' and 'too much' did not provide enough information to establish whether preference for treatment or trial participation were an issue for families.

Qualitative findings suggested that targeted training that focused on equipoise and exploring families' treatment preferences, had beneficial effects on recruitment to the MAGENTA, FITNET-NHS and CONTRACT trials. There was no evidence of high numbers of participants withdrawing immediately post randomisation during each of the four trials. Feedback from families (via interview) suggested that they were happy with the way in which each trial was presented, discussed and conducted. However,

rises in recruitment in each of the four trials cannot be solely attributed to the training programmes, patterns of improvement and increases in recruitment post training could be accounted for via alternative explanations. Regression to the mean [631] is a statistical phenomenon whereby a variable (e.g. recruitment to trial) may be extreme in one instance, (month) but is likely to be closer to the average on second measurement, or vice versa: *'Any intervention aimed at a group or characteristic that is very different from the average will appear to be successful because of regression to the mean'.* [632] [pg. 1083] Since regression to the mean is likely to occur in small, non-random samples, it must be considered that some of the more 'extreme' differences or improvements in recruitment post training could be accounted for by regression to the mean.

Recruiters may have gained confidence and become more skilled at discussing the RCT as each of the trials progressed. As an RCT progresses recruiters are likely to become more familiar with the inclusion and eligibility criteria, trial materials, and other related trial information that they routinely verbally discuss with participants and family members. This might result in more succinct and successful communication strategies, resulting in more families consenting to RCT involvement. It could also be argued that 'tips for recruitment' documents kept locally accounted for patterns of improvement in recruiters' ability to successfully recruit, not the structured training delivered by researchers at regular intervals throughout each RCT. However, the pattern of change (increasing after training and then reducing as the time since training increased) and consistency across trials, combined with the qualitative work suggests the training did contribute to patterns of improved recruitment.

5.4.2 Retention: Preference and ongoing participation

SMILE

Fifteen participants (15%) in the SMILE RCT did not receive their allocated intervention as per protocol (n=12, 24% in the Specialist Medical Care plus Lightning Process group, and n=3, 6% in the Specialist Medical Care group). Three participants received specialist medical care and one day of the Lightning Process course (6%), and nine only received specialist medical care (18%). Two participants in the specialist medical care group paid to complete the Lightning Process course (4%). One participant (2%) did not receive any specialist medical care and paid to complete the Lightning Process course.

Feedback from the mother of one young person who did not want to attend the Lightning Process course despite being randomised to that treatment group suggested their reason for non-attendance was partly related to the treatment approach:

> *Mum S76:…he read the book and didn't like the approach, he felt it was brain washing*
>
> *Email feedback SMILE Specialist Medical Care plus Lightning Process 15yrs Male*

This does not provide evidence for a preference *between* treatment groups. Neither parent or young person expressed a preference for treatment during their recruitment consultation, but the family did express some worries about the amount of travel needed to get to the course.

Although response to outcome measures has not been analysed in relation to retention in this thesis, it is worth noting that 81 participants (81%) completed the primary SMILE outcome (SF-36 Physical Function) at the six-month point in the trial. Fewer participants in the Specialist Medical Care group returned primary outcome measures at six months, which could indicate dissatisfaction with treatment. This should not be confused with having a specific 'preference' for one treatment group in comparison to another. Non-return of outcome measures could also be related to questionnaire burden or a variety of other factors.

MAGENTA

Six participants (43% of those who discontinued a trial intervention within six-months of randomisation, 8% of those randomised), gave preference as a reason for discontinuing their trial intervention (Table 5:11). Although the number of participants discontinuing treatment (for all reported reasons) was equal between intervention groups, the number discontinuing because of a reported preference for the opposite intervention was higher in the activity management group. Five participants (13%) in the activity management group discontinued treatment because they had a preference for Graded exercise Therapy. Only one participant in the Graded Exercise Therapy group discontinued their allocated intervention because they had a preference for activity management (3%).

Although discontinued treatment does not provide evidence for a preference between intervention groups at trial outset, some families who had expressed a preference at outset (e.g. participant and parents M35) did go on to discontinue their

allocated (non-preferred) intervention. However, parent (and participant) preferences for treatment at the point they discontinued treatment, did not always appear to correspond with the preference they expressed during their recruitment consultation. Although family M70 stated 'preference for other group' as a reason for discontinued treatment, when given the participant's allocation mum stated: *"I actually feel better about that one, [15yr old female, randomised to activity management] than the other one [Graded Exercise Therapy]*" This participant went on to discontinue treatment their parent appeared to prefer, or was at least satisfied with at trial outset.

One family reported past experience of the intervention (in addition to preference) as a reason for discontinuing their allocated trial intervention:

> *[Participant 28] started on the activity diary choice in the MAGENTA trial, but felt after a time that a year already of doing this had got her nowhere. [health professional] was supportive of her trying Graded Exercise Therapy, so [participant 28] left the trial.*
>
> *Email from mother 28: MAGENTA activity management 14yrs Female*

After six months of treatment (and the six-month primary outcome point) only one family in the activity management group (20% of those who discontinued a trial intervention) reported preference as their reason for discontinuation, (Table 5:12). However, It was explicitly stated in the parent and patient information leaflets that young people could "change treatment" at the six-month point if they chose to, (see: Appendix 4 Information leaflet for young people (12-17yrs) and Information leaflet for parents - 'Are there any disadvantages to taking part in this study?'). Feedback after the six-month point, reported via health professionals included statements from

participants wishing to ‘swap’ treatments or continue with their allocated treatment ‘in the background’ whilst using elements of the ‘opposite’ trial treatment at the same time:

> *[Participant 62] was not able to sustain Graded Exercise Therapy on a daily basis. She was therefore not making progress. As it has been 6 months she wanted to swap [Email from health professional]*

Thirty-five participants were due to complete their six-month follow-up questionnaires during the first 12 months of the trial and 32 participants (91%) completed the six-month primary outcome measures.

Table 5:11 MAGENTA feasibility trial: Participants who discontinued treatment within six months of randomisation

Intervention group	Patient age at consent	Sex	Months between randomisation and discontinued treatment (Rounded down)	not recovering in allocated intervention group	deteriorating in allocated intervention group	preference for other intervention group	trial burden	Received treatment (not GET/AM) outside of the trial	Does not want any further clinical treatment with the service	Other	Participant discontinued treatment	Participant withdrawn from trial follow-up
AM	15	Female	0			✓	✓				Y	Y
AM	16	Male	1	✓		✓					Y	
AM	12	Female	1					✓	✓		Y	Y
AM	14	Female	2	✓		✓					Y	
AM	17	Female	2				✓				Y	Y
AM	16	Female	2			✓	✓				Y	Y
AM	14	Male	3			✓					Y	
GET	16	Female	1			✓					Y	
GET	12	Female	1		✓						Y	
GET	12	Male	1						✓		Y	
GET	14	Female	1					✓	✓		Y	Y
GET	16	Female	2							✓	Y	
GET	15	Female	3				✓				Y	Y
GET	14	Female	3				✓				Y	Y

Table 5:12 MAGENTA feasibility trial: Participants who crossed to opposite treatment group after six months of treatment

Intervention group	Patient age at consent	Sex	Months between randomisation and discontinued treatment (Rounded down)	not recovering in allocated intervention group	deteriorating in allocated intervention group	preference for other intervention group	trial burden	Received treatment (not GET/AM) outside of the trial	Does not want any further clinical treatment with the service	Other	Participant discontinued treatment	Participant withdrawn from trial follow-up
AM	17	Female	6			✓					Y	
AM	15	Male	7				✓				N	Y
AM	15	Male	9	✓			✓				Y	Y
GET	10	Female	6	✓							Y	
GET	15	Female	6	✓							Y	

FITNET-NHS

Retention and follow-up rates were high during the internal pilot phase of the FITNET-NHS trial. Seven participants (8% of those randomised) discontinued their trial intervention: one at three-months, four at the six-month point and two after the six-month point. Six participants in the online CBT intervention group discontinued treatment (15%) and one discontinued skype activity management (2%). One (2%) of the participants in the online CBT group also withdrew from trial/research follow-up. None of the participants who discontinued treatment gave preference as a reason, however two reported that they were unsatisfied with their treatment program and both were categorised as 'deteriorating in allocated group'. Further notes on these family's reasons for withdrawal stated that one family were, *"not at all confident in the online CBT approach… she [participant] was quite sarcastic about the approach".* The other had found that, *"symptoms worsening rather than improving, going to be offered face to face assessment"*. Neither family continued to receive treatment from the Specialist Paediatric CFS/ME Service. There was no further qualitative interview data available from families who discontinued treatment. (see: Table 5.13)

Table 5:13 FITNET-NHS Internal pilot: Participants recruited to internal pilot who discontinued treatment

Participants recruited to the internal pilot who withdrew from treatment and/or study												
Intervention group	**Patient age at consent**	**Sex**	**Months between randomisation and discontinued treatment (Rounded down)**	**school (GCSEs, A Levels)**	**trial burden**	**external events (holidays)**	**not recovering in allocated intervention group**	**deteriorating in allocated intervention group**	**preference for other intervention group**	**received treatment (not FITNET/AM) outside of the trial)**	**does not want any further clinical treatment with the service**	**Participant withdrawn from trial follow-up**
AM	15	Female	8					✓				
FITNET	16	Female	3									Y
FITNET	13	Male	6	✓								
FITNET	16	Female	6				✓				✓	
FITNET	15	Female	6		✓					✓	✓	
FITNET	16	Female	6					✓				
FITNET	12	Female	9		✓		✓				✓	

CONTRACT

One family declined treatment immediately after randomisation to the surgical intervention because they wanted antibiotic treatment (2% of those randomised). Eight participants in the non-operative arm received an appendicectomy due to treatment failure (14% of those randomised). It is not known to what extent decisions to discontinue non-operative treatment were initiated or facilitated by young people, parents, nurses or surgeons when participants switched to appendectomy. Neither is it clear whether family members or health professionals made the decision to treat those with recurrent appendicitis with an operation when they returned to the hospital post discharge (seven, 24% of participants randomised to the non-operative arm). Two young people who participated in interviews reported that they were successfully treated with further antibiotics when they returned to hospital with recurrent symptoms post discharge. Treatment of recurrence with antibiotics was only apparent at one of the three participating sites.

The impact of treatment preference on retention in paediatric RCTs

It is not possible to be certain that preferences formed prior to, or during recruitment consultations had an impact on retention. There are several reasons that make these analyses difficult, including the length of time from randomisation to discontinuation of treatment in the behavioural trials (SMILE, MAGENTA and FITNET-NHS). There are multiple additional factors that might influence retention (e.g. disease activity, interaction with health professionals, school or family issues, ongoing satisfaction with trial intervention and trial burden). In addition, the overall number of participants discontinuing treatment was relatively low and varied between the four trials.

Discontinuation (of trial interventions and/or trial withdrawal) because of a reported preference for the opposite trial intervention was most apparent in the MAGENTA RCT, seven families (37% of those who discontinued a trial intervention) reporting this as a reason. However, families could provide multiple reasons, and trial burden was also reported by the same number of families (n=7, 37%). Only two families provided both preference for treatment and burden as reasons for discontinuation. The stated option of, 'having the other treatment after six months' in MAGENTA PILs may have influenced families' decision-making and engagement in relation to continuing with their allocated intervention.

No families reported preference for treatment when discontinuing interventions or withdrawing from the FITNET-NHS RCT. Trial context (e.g. the lack of an easily accessible local paediatric CFS/ME service for FITNET-NHS participants), may have increased families' willingness to participate and engage with trial interventions. Although there was some qualitative evidence to suggest that preference for treatment resulted in families withdrawing post-randomisation (CONTRACT) and discontinuing treatment after reading about or receiving some of the allocated intervention (SMILE), these preferences at the time of discontinuation cannot be linked directly to preferences expressed during recruitment consultations. The extent to which preferences for treatment interact with and influence young people and their parents continued engagement with trial treatment interventions remains unclear.

5.5 Chapter summary of findings

This chapter explored the ways in which young people and parents' preferences for treatment affected recruitment rates and trial participation in four paediatric RCTs: SMILE, MAGENTA, FITNET-NHS and CONTRACT. Exploration of how and when preferences were expressed found that expressions of preference occurred while families made decisions about taking part in research, when they reacted to the outcome of randomisation, and when they decided to discontinue treatment or withdraw from one of the RCTs.

Parent preference often became more apparent immediately post-randomisation, when preferences were more overtly expressed by parents in response to information about their child's intervention group allocation. This was more apparent during the SMILE and FITNET-NHS trials. Strength or conviction with which preference for treatment was expressed (before or after randomisation) changed depending on whether similar treatment was accessible outside the trial - preference discussions were more apparent before randomisation during the MAGENTA RCT where similar interventions were also accessible outside the trial.

Young people were less likely than their parents to express preferences for treatment during recruitment consultations, with parents also expressing stronger preferences than young people for specific interventions. At times, the preferences of young people and their parents differed, as did preferences between parents when both mum and dad were present.

Recruitment conversations were split roughly into four separate stages: an initial mention, main consultation, obtaining consent and randomisation. Rarely were all conversations recorded and available for analyses. However, the importance of recording as many interactions with families as possible (particularly families' responses to randomisation) became apparent when seeking to understand preferences for treatment, and which family member(s), (young person, mum or dad) had preferences.

During the 'main' recruitment consultation, young people and parents often discussed preferences for treatment in relation to motivations or reservations about taking part in the trial. However, discussions about preference were not specific to one 'area' of the consultation (e.g. when discussing treatment) and were also apparent during discussions about randomisation or recovery. Recovery was the main priority for families (young people and parents) but they also frequently discussed altruism as a motivation for taking part in the trials.

Many families consented to involvement in paediatric RCTs despite having preferences for a specific intervention group, post-randomisation interviews confirmed that some families were not in equipoise, but still decided to participate. Preferences for the 'active' or 'control' treatment groups were apparent depending on trial context, with 'new' or 'experimental' treatments more likely to be perceived as potentially harmful by CONTRACT and MAGENTA trial parents, as opposed to more positive perceptions of 'active' treatments in the SMILE and FITNET-NHS trials.

Data relating to preference for treatment and its impact on participant flow, recruitment rates, and retention were reported in Section 5.4. The number of eligible families declining participation in these four paediatric trials because of preferences (at recruitment) ranged from 4-27% (see: Table 5.10). Although preference for treatment was a consistent reason for trial decline, all four trials were able to successfully recruit participants. The three paediatric CFS/ME trials successfully converted to full trial status, and the CONTRACT feasibility RCT met the HTA target of recruiting between 52-65 patients over a 12-month period, (57 participants were randomised). Preference was reported when families declined treatment immediately after randomisation, (CONTRACT) and discontinued and crossed between intervention groups (SMILE and MAGENTA). However, figures relating to preference and discontinued trial interventions / trial withdrawal were problematic and will be discussed further in Chapter 6.

Health professionals initially responded to preferences by accepting them at face value, some of the language they used to communicate trial rationale and treatments did not convey equipoise between treatment groups, and potentially reinforced families' preferences. Training for health professionals included tips on how to explore preferences for treatment, offer balanced information about intervention groups, and how to communicate and discuss trial rationale, uncertainty and randomisation. This training contributed to an improvement in observed recruitment rates of eligible young people.

Some recruiters and health professionals providing ongoing care may have found it difficult to explore families' preferences and highlight the equivalence of trial interventions because they reported a lack of personal equipoise about one intervention offered in the trial. Periodic training for recruiters that focused on communicating equipoise and exploring preference provided examples of the way in which training influenced and changed communication practices in each RCT and appeared to have a positive effect on recruitment figures. There were more examples of recruiters' using open questions and exploring families' preferences for treatment after training. This included exploration of reasons for preference, offering balanced information about treatment groups and changing language which might convey recruiter biases for treatment or reinforce existing family preferences. Health professionals recruiting to paediatric trials valued training and feedback.

Chapter 6: Discussion

6.1 Overview of Chapter

This final chapter includes a comprehensive review of the findings reported in Chapter 5 and acts as a starting point for further exploration of treatment preference and equipoise in paediatric RCTs. I will reflect on the qualitative methods used and discuss findings in the context of existing literature. A discussion of findings from the systematic literature review and qualitative synthesis can be found in Chapter 4, Section 4.4. Finally, this chapter highlights the strengths, and limitations of my research, and implications for future research in this area.

6.2 Context of findings

6.2.1 Using qualitative research methods in RCTs

Only 12% of trials reported the use of embedded qualitative methods to improve recruitment between 2008 and 2010. [633] This figure is likely to be smaller in paediatric trials. It is important to improve the design and conduct of trials which recruit young people and children by ensuring that recruitment processes are transparent. [175] As discussed in Chapter One, recruitment problems can delay or prevent trial completion with adult [124, 179-187, 634-637] and paediatric trial populations. [188, 217, 219, 220, 587, 638] The use of qualitative research methods in RCTs - particularly in relation to improving rates of recruitment and retention - improves trial conduct. [123, 182, 198-202, 206, 207, 639, 640]

Elements of the 'QRI approach' (see: Section 2.2) [408] were applied in the four paediatric trials described in this thesis, to explore and understand treatment preferences and promote good communication practices. I have demonstrated that these embedded qualitative methods (e.g. tracking participant flow, analyses of audio-recorded recruitment consultations and interview data to understand preference, and individualised trial training to improve communication about preference related issues), can be used effectively in varied paediatric RCT settings (with acute and long-term paediatric health conditions). Qualitative findings reported in the current thesis were observed alongside increases in recruitment after training sessions that incorporated suggestions on how to explore expressed preferences and convey equipoise. (see: Chapter 5, Figures 5:4-5:6). [641, 642]

6.2.2 The impact of preference on trial recruitment

The data I collected for this thesis has identified that recruitment to paediatric RCTs is impacted by parents' and young peoples' preferences for treatment (see: Sections 4.2-4.3 and 5.3-5.4). This is consistent with findings from adult trials, whereby preference for treatment had been shown to influence recruitment. [62, 279, 287-289, 292, 540] The ProtecT study [98, 123, 404, 405, 643] found that patients' preferences for treatment diminished after targeted discussion and exploration of preference with a recruiter. [247, 405, 407, 409] The composition of paediatric trial samples could be affected if families decline trials because of preference for treatment, particularly if families of young people with strong preferences differ from those who are indifferent about trial interventions (e.g. those with strong preferences

may have been ill for longer). [67, 644, 645] Slow recruitment can also result in the need for trial extension [66, 604] or closure. [584, 600]

It was previously not clear whether preference was consistently cited as a reason for trial decline with a paediatric population, and in what way preference impacted recruitment. Past research has reported a number of factors which might act as facilitators or barriers to paediatric RCT participation. [93, 94, 205, 317, 319, 328, 365, 622] The way in which preference for treatment impacts paediatric RCTs is complex, i.e. those with preferences do not simply decline trial participation. These findings are consistent with systematic reviews investigating the effects of preference on retention in RCTs. [213, 279, 289]

Findings from this thesis indicated that treatment preference was discussed in the context of perceived risks and benefit, (see: Sections 4.2-4.3 and 5.3-5.4) therefore highlighting the importance of preference consideration in recruitment consultations at all points in the conversation. An honest discussion of RCT risks and benefits has been cited in previous research as important to parents considering RCT participation for their child. [214, 224, 229-232] Mis-perceptions of risk also highlight the way in which perception of trial interventions and preference issues relate to research integrity, parents might incorrectly assume being involved in a trial poses no risk: *"They are the specialists. They know what they are doing"* [270] [pg. 150]

My findings also support existing literature which has linked preferences for treatment to perceptions of trial intervention groups being 'control' or 'experimental' (see: Active versus Control and Experimental versus Standard treatment). The potential for perceptions of treatment to act as barriers or facilitators to trial participation has been highlighted in past literature as important when discussing trial participation. [74, 646, 647] Parents have raised concern around the type of interventions offered in RCTs, e.g. an intervention which is a change from 'current' or 'standard' recommended practice, [225] and factors associated with perceived disparity between intervention groups linked to a lack of equipoise. [227] Preferences for the 'active' or 'control' intervention differed depending on trial context. Trials with a 'normal' or 'control' intervention (surgery) were preferred in the acute care context. Trying something 'new' (Graded Exercise Therapy) was viewed negatively by some parents concerned about potential harm during the MAGENTA RCT. Impact on wider family circumstances, (e.g. siblings, planned activities and holidays) and close family members past experience of treatment (e.g. negative experiences of appendicitis) were important factors discussed by families who declined the CONTRACT RCT. However, the extent to which wider family members facilitate or inhibit RCT participation remains unclear. [234-236]

6.2.3 The impact of preferences on trial retention

I have identified that parents and young people entered trials despite their preference for treatment. If families enter a trial despite having preferences for treatment, those randomised to a non-preferred intervention group may be less willing to adhere to treatment protocols and subsequently drop out. This could lead

to bias. [644] Data collected for this thesis also identified that continued participation in paediatric RCTs was impacted by parents' and young peoples' preferences for treatment (see: Retention: Preference and ongoing participation). However, not all of those who expressed preferences before randomisation went on to discontinue trial interventions or withdraw from trial outcomes, particularly in the FITNET-NHS trial.

While it may seem obvious that treatment preference may influence retention (particularly with those receiving a long-term intervention), the evidence relating to the way in which preferences affect continued trial participation and satisfaction with treatment is not clear. [279, 289, 292, 648-653] Collaboration between parent and child has been recognised as a crucial facilitating factor in terms of retention in trials which investigate long-term conditions, [270, 353-356] therefore the influence of parents in terms of their preferences for trial interventions should also be considered as a trial proceeds, particularly when parents are also responsible for completing outcome measures (e.g. measures of health economic impact).

The role of health professionals' ongoing equipoise during the delivery of long-term interventions, and the extent to which this impacted families' decisions to discontinue RCT interventions, was also unclear (particularly during the MAGNETA RCT). Long-term health conditions such as CFS/ME and diabetes involve RCT interventions which require buy-in, motivation and effort, or a change in behaviour from those participating. [78, 359, 360] Not only does this require commitment from participants, it also requires commitment from the parents of participants, as well as the health professionals delivering the on-going intervention programme.

A recent article found that few PILs (n = 6, 12%) informed participants that they would be asked (if willing) to provide a reason if they decided to withdraw from the trial. RCT documents (consent forms) rarely included information about the importance of equipoise (n = 3, 6%) or the difference between 'discontinuing trial interventions' and 'withdrawing' from the trial (completion of outcome measures). [654] If this information was presented in an accessible format in written PILs, health professionals approaching participants and families might be more willing to verbally explore reasons for decline, discontinued treatment and/or withdrawal with potential participants and their families (see: Section: 5.4.1: SMILE and Section 5.4.2 MAGENTA).

6.2.4 The impact of preference on trial design and interventions

Trial dimensions which may impact treatment preference in paediatric RCTs include: a) trials requiring commitment to an on-going intervention or behavioural programme, versus those that have an immediate or short-term intervention, such as non-behavioural trials, b) trials that can be blinded (versus those that are open) and c) trials offering treatment that can be obtained outside the trial compared to those where a new treatment can only be obtained within the trial.

Trials requiring commitment to an on-going intervention or behavioural programme

RCTs requiring commitment to an on-going intervention or behavioural programme are more likely to be impacted by preference for treatment, because preferences can

have an ongoing effect on the retention of participants. In circumstances where families (young people and/or parents) do not receive a preferred treatment, motivation, adherence and commitment to the allocated non-preferred intervention, and completion of trial questionnaires may be more challenging for them to engage with over the extended period needed for such an intervention to demonstrate effective changes in behaviour (e.g. when the primary outcome point is six months). Thus, preference effects were more pertinent to the CFS/ME trials included in this thesis. The SMILE, MAGENTA and FITNET-NHS RCTs all required behaviour change and a significant level of physical and/or mental commitment and input from young people (and their parents) post-randomisation, for an extended period of time (12 months). This issue can be generalised to other paediatric (and adult) trials exploring interventions for other long-term conditions, (such as asthma, diabetes and obesity) where motivation and commitment from young people and their parent(s) is of paramount importance to intervention adherence and completion of RCT outcome measures. [237, 526, 655]

Blinded versus open RCTs

Although open (unblinded) trials are considered ‘at risk’ of bias, [79] and the possibility of receiving a non-preferred treatment can result in some eligible patients refusing these RCTs, [292] open RCTs typically have higher consent rates as patients like to know which treatment they will receive. [80-82, 213] Past research into paediatric RCTs has shown that when study groups are perceived as very different in terms of effectiveness (e.g. placebo versus active treatment) decision-making in relation to consent to trial is more problematic for parents, particularly

when a child is seriously ill. [97, 218, 227, 233] Open RCTs investigating markedly different treatments taking place soon after randomisation, (e.g. surgical versus non-surgical interventions are also susceptible to preference effects at the point of recruitment. [84]

Preferences for treatment can affect adherence to treatment groups post-randomisation in open RCTs. [62, 287-289] If a patient is not in equipoise about treatments offered in a trial but still opts to participate, they will be assigned their preferred or non-preferred treatment. This is an issue because the direction in which preference effects influence commitment and adherence to treatment interventions in RCTs is not straight forward. As might be expected, allocation of a non-preferred treatment can result in disappointment and resentful demoralisation in some instances. [62, 292] However, participants who receive their non-preferred trial group have been found to be more likely to return outcome measures in adult trials. [289] Varied post-randomisation preference effects should not be overlooked in open paediatric RCTs, where findings have shown non-preferred trial arms have either; been accepted without having a negative effect on retention, [656] or become the preferred treatment after experience of the intervention, despite a preference for the opposing treatment approach prior to randomisation. [291]

All of the trials analysed in this thesis were open because blinding was not feasible. Blinding is particularly difficult for any RCT which compares and evaluates behavioural interventions where participants are asked to follow a specific programme of treatment over a long time period. [78, 358-360] None of the RCTs

under investigation had significant problems recruiting the specified number of participants during feasibility and internal pilot phases. [204, 657-659] However, 27% of eligible families declined the CONTRACT RCT because of preference for a surgical intervention, which lends weight to finding that markedly different surgical versus non-surgical intervention RCTs can be susceptible to preference effects at the point of recruitment. [84]

Availability of treatment outside an RCT

The availability of treatment outside an RCT can also have an impact upon the effects of preference (see: Ethical issues and participation in paediatric RCTs). Concerns around the type of treatment offered in RCTs, e.g. a treatment that is not familiar or is a change from 'current' recommended or accepted treatment, have been observed as a barrier to recruitment in previous research. [225] However, young people and their parents have reported new or free access to treatment as a positive reason for participating in RCTs, particularly for those on low incomes or in countries where healthcare is not free at the point of need. [93, 120] When an attractive, costly or new intervention is not yet available outside an RCT, (e.g. the Lightning Process, or online treatment for CFS/ME, antibiotic treatment for appendicitis) families reported that they had 'nothing to lose' by participating in the RCT if they wanted the routinely 'unavailable' treatment. However, many then felt disappointed when their child was not allocated the preferred unavailable treatment. A high proportion of families eligible for the MAGENTA RCT declined because they perceived 'more as better' i.e. their child could receive 'a bit of both', (activity management and GET interventions) outside the RCT.

At times during interviews health professionals also expressed the view that 'more' or 'both' activity management and GET was preferred. Issues relating to the rationale for including specified treatment pathways in an RCT should be discussed openly with clinical teams prior to commencing a trial in order to reinforce team equipoise going forward, especially if treatments continue for a long period of time post-randomisation. [197, 457] Little is known about the way in which preference impacts intervention adherence and the completion of outcome measures in regard to whether or not treatment is available outside an RCT. [93, 120, 270, 309, 312]

6.2.5 Equipoise, uncertainty and competing moral demands

Findings reported in this thesis (Chapter 5 - Understanding how recruiters' respond to treatment preferences in paediatric trials) indicate that prior to training descriptions of trial interventions were unbalanced. Recruiters referred to one intervention as the '*gold standard*' (surgery) or '*the best*' (face-to-face treatment for CFS/ME, FITNET-NHS). Since RCT recruitment is mainly carried out by those who also have day-to-day clinical responsibilities, this has important implications - health professionals taking on the additional role of 'recruiter' may not consciously view themselves as 'researchers' when they participate in trial related activities. [260-262] Interview feedback highlighted that health professionals often accept the concept of 'collective' equipoise, that there is a lack of current evidence-base, and that there is a need for randomisation to ensure methodological rigour. However, after randomisation in the MAGENTA and FITNET-NHS trials some recruiters also disclosed 'personal opinions' based on intuition relating to allocated intervention (e.g. I think you'll be well suited to that one). During CFS/ME trials some health professionals expressed an allegiance to their primary 'specialty' or the intervention that they deliver on a

more regular basis (e.g. surgery or activity management). This is consistent with descriptions of equipoise in the adult literature, where a lack of personal equipoise at recruitment (expressed inadvertently via personal or expert opinion) can undermine discussions of collective equipoise. [177, 262, 660, 661]

Fluctuation in personal and collective (clinical) equipoise poses a challenge in trials research. Levels of equipoise will change over time at an individual and group level as trials progress. [255] Health professionals recruiting to CFS/ME trials reported occasions where they felt that they knew patients 'needed' a certain approach (e.g. Graded Exercise Therapy or activity management) at a specific point in time, drawing on knowledge from past experience and specialist expertise. During the CONTRACT trial an incident of antibiotic 'treatment failure' early during recruitment resulted in the loss of equipoise for some members at one recruiting site. This highlights the relevance of Gifford's 'sliding scale' approach to equipoise, [255] where young people, parents and health professionals may be 'in equipoise' to differing degrees and at different points in time. Lack of personal equipoise, and the effect of 'disclosure' by recruiters or members of the wider clinical team may have an effect on the treatment perceptions of parents and young people at any point in the trial process, therefore the effects on retention are less clear.

Findings from the line of argument developed via the meta-ethnographic parent data, (Chapter 4) and parent/recruiter data from the four collaborating RCTs (Chapter 5) highlighted the emotional nature of discussions during paediatric RCT recruitment consultations. Past literature has highlighted that health beliefs are situated in wider

social discourses, and accounts of parents' experiences of decision-making about their child's trial participation can be linked to the 'rhetoric of morality'. [662] Trial participation takes place against the backdrop of competing moral demands, since paediatric RCTs have the added dimension of parents consenting for an intervention on behalf of, or in collaboration with their child. This results in 'clashing ethical norms' when parents struggle with an overwhelming wish to do the best for their child, whilst also drawing upon wider cultural discourses (e.g. altruism) when discussing participation in research. [663]

Data from the four collaborating trials (Chapter 5) also supported the line of argument. Parents' language conveys their vulnerability, and the accountability they feel in relation to making a '*wise*' or a '*poor*' decision. [325, 664] Parents also convey *'worry'* and the potential for judgement*, 'thinking you're doing the wrong thing*'. [97] These findings are supported by wider research into parent decision-making for elective surgery in the field of cleft lip and/or palate. [665] In the context of elective surgery, parent decision-making was framed in terms of emotional, social and cultural expectations, all of which had a key influence on parental motivation: *"parents appeal to 'doing the right thing' as part of a perceived 'moral' obligation of being a 'good' parent".* [665] [pg. 802] Establishing the legitimacy of actions and beliefs is also a key aspect of the decision-making process for parents who decide to participate: '*I do actually really believe in research… even if we end up as the control group'* (SMILE RCT), and particularly for those who decline participation: "*I just don't feel that I can take the risk with my own child, I think if it was me I might give it a go"* (MAGENTA RCT).

Those recruiting to CONTRACT reported feeling '*really upset'* and *'guilty'* when those randomised to the antibiotic group did not respond to treatment. It was suggested during interview feedback from those recruiting to the CONTRACT trial that some members of the wider teams *'didn't like'* or believed that antibiotic treatment was '*ineffective*'. It was unclear who had initiated discontinuation of antibiotic treatment during the CONTRACT trial - whether it was instigated as 'necessary' by surgeons, 'requested' by parents, or by the young people themselves. Health professionals also used language highlighting their struggle with the competing demands of the expert clinician providing the best care for their patient, coupled with the uncertainty required in both the discussion of RCT participation and the allocation of treatment via randomisation: *"you're admitting to patients and families… we don't know what the effective treatments are"* [Health Professional ME]. Findings outlined in this thesis demonstrate that the attitudes and personal opinions of health professionals affect the way in which interventions are discussed with families at recruitment, and during intervention delivery. This is likely to influence families' preferences for treatment and continued participation as a trial progresses - however the mechanisms of this interaction are not yet clearly defined.

Past literature has reported the 'emotional' response of recruiters and parents when dealing with disappointment with an allocated intervention group after randomisation. [109, 457] Recruiters (surgeons and research nurses) particularly valued training that focussed on conveying equipoise, rationale for randomisation, and exploring preferences for treatment. Ongoing training and support appears beneficial to recruiters and further research should be carried out into the emotional aspects and

competing demands of RCT recruitment, further developing training courses offered to those recruiting to RCTs. [246, 641]

My findings also suggested that many families were not in equipoise when they consented to trial participation - this has also been reported in the adult literature. [286] If families consent to randomisation despite reporting preference for treatment (before or after randomisation) they may be more susceptible to the comments and views of health professionals who lack personal equipoise later in the trial process. At times it was difficult for health professionals in the MAGENTA trial to provide treatment 'as per protocol', particularly when they perceived that young peoples' treatment needs had changed e.g. *"they now need to do exercise"*. This was reported as a particular issue for health professionals with substantial experience of treating young people, using a specific approach/technique over a number of years. If a procedure has been routine for many years, it may be more challenging to train health professionals to discuss alternatives to that treatment from a place of equipoise. [666] Although there may be collective uncertainty among health professionals about the effectiveness of interventions in a specific clinical area, both health professionals and trialists may 'suspect' or have anecdotal evidence that preferences exist in the wider patient community. [667] [668] [669]

Trials that have surgical and non-surgical intervention groups may be particularly susceptible to preferences for treatment where, prospective participants and society at large have apprehensions about not 'removing' tumours or infected tissue (such as tonsils or the appendix). [66] This may be observed with illnesses or diseases

where the public have widely accepted views about what is the best course of action in the case of cancer (tumour removal to provide a cure) or appendicitis (removal of the infected organ to avoid rupture and more serious prolonged illness). This may also be relevant to other diagnosed conditions, such as CFS/ME, where patient and support groups campaign against certain treatment approaches (e.g. Graded Exercise Therapy and the Lightning Process). The effect of these 'discourses' on the way in which equipoise is communicated to families has not been widely explored, but is likely to be a two-way process, resulting in changes in health professionals' views and equipoise as they encounter families with entrenched views. In such circumstances, health professionals might draw on discourses of autonomy and patient choice to legitimise their lack of equipoise, highlighting a family's preference for treatment as the reason why trial participation is not appropriate. [112, 670]

Uncertainty which arose from the use of randomisation to determine a treatment pathway offered in the RCTs was problematic for some health professionals (see: Discussing uncertainty and equipoise: what would you do?).

Uncertainty about the most effective available treatment led parents to draw upon other sources of knowledge, such as past experience of treatment (particularly in the context of appendicitis), and some asked recruiters what they would do if it were their child in this situation. This has been reported in the wider paediatric trials literature, [325] and suggests that parents seek guidance and personal reassurance from the recruiter. The issue of disclosure is difficult for recruiters and trialists, since the patient may view 'a hunch' or a 'personal opinion' as an informed evidence-based clinical opinion which they can trust and use as a firm basis for decision-making.

Health professionals recruiting to all the trials under investigation in this thesis reported interpretation of eligibility criteria as a factor affecting recruitment to trial. Recruiters (particularly during the CONTRACT RCT) discussed feeling more comfortable when recruiting patients who presented within a certain subset of the eligibility criteria - those who had less severe symptoms. Previously this was described as, "*the group in the 'middle' with unremarkable clinical and socio-demographic features*". [262] [pg. 260] Those at either end of the eligibility spectrum had the potential to be excluded on 'subjective' or 'softer' grounds based on 'hunches' and 'bias'. Examples included - psychological issues in CFS/ME trials, or other co-morbid physical conditions when treating appendicitis. [262] Support for this finding is available in paediatric RCTs [260, 273] and in the wider theoretical literature. [31, 102, 274-277]

Interviews with health professionals suggested they were committed to the RCTs to varying degrees, believing that they offered '*an answer to the question'* and would move evidence-based practice forward in areas that required further exploration. However, my findings suggest that the severity of the condition under investigation, perceived trial or intervention burden, and the seriousness of outcome may be factors influencing both individual and collective team equipoise. This highlights the need for pre-trial and ongoing team meetings and discussions, where team members can openly raise issues or gain clarification in relation to trial eligibility criteria and trial intervention groups (see: Recommendations and implications for future research). The following conceptual model (Figure 6:1) provides a visual map of the way in which health professionals might act as gatekeepers to RCT research, determining whether or not a trial is burdensome or in the best interests of the

patient, and determining risk versus reward on their behalf. At the same time a patient's health status, attitudes and engagement with the health professional will influence their perceptions of risk versus reward in participating in the trial.

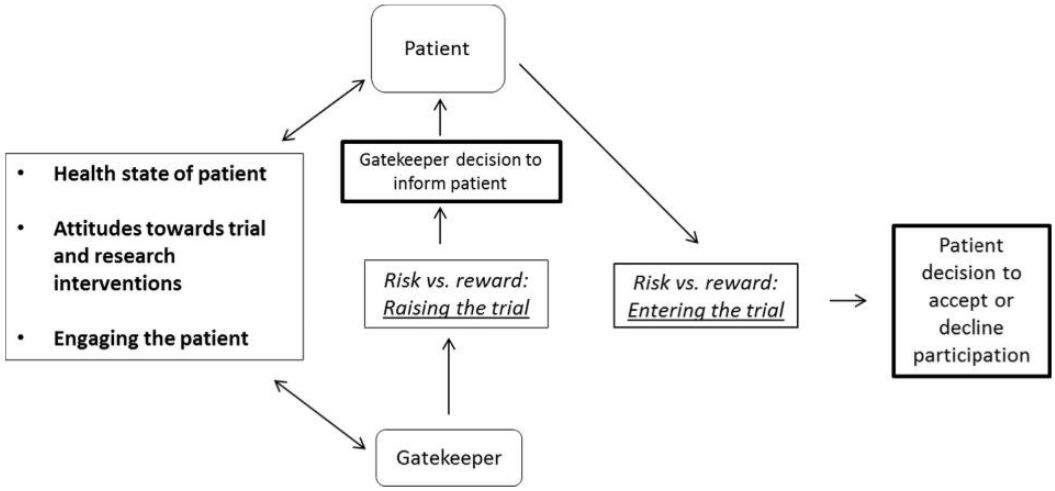


Figure 6:1 Conceptual framework of factors influencing the decision to participate

Hughes-Morley, Young, Waheed, Small and Bower (2015)

6.2.6 How do these findings map on to an existing model of patient preference and decision-making?

My findings highlight the complex and dynamic nature of preference for treatment and decision-making in the context of paediatric trial recruitment and participation. My findings can be 'mapped' onto the existing conceptual model of patient preference developed by Bower and colleagues. [279, 294]

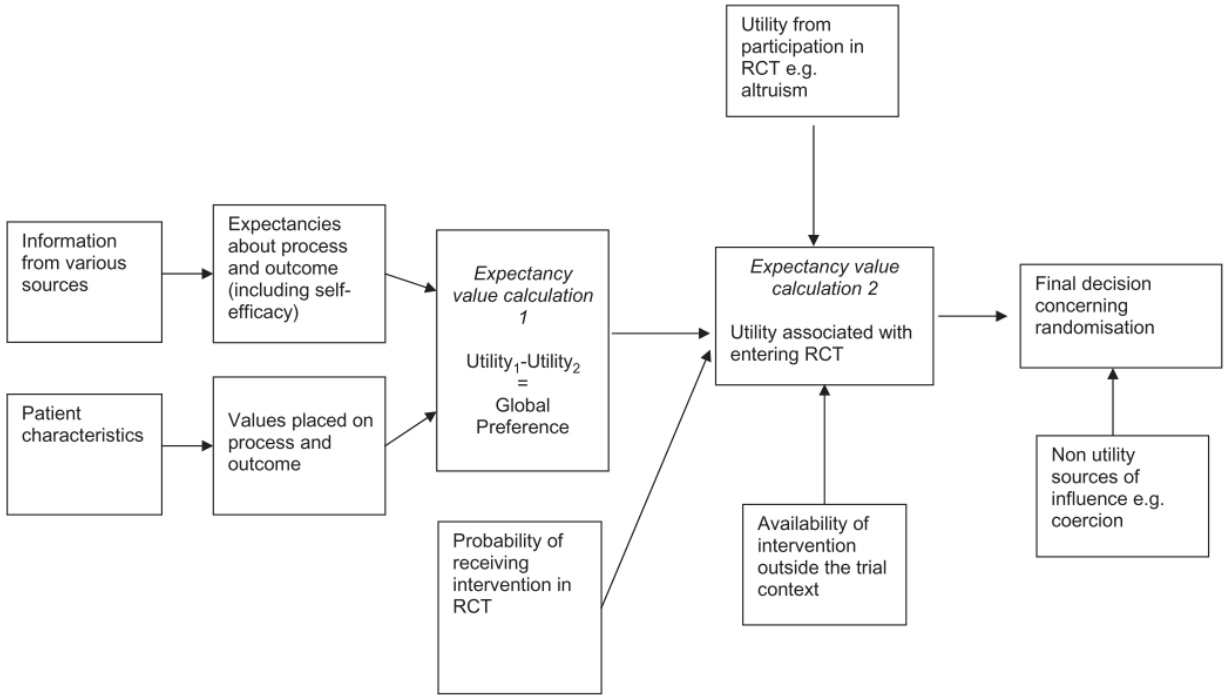


Figure 6:2 A model of patient preference and decision-making

Bower, King, Nazareth, Lampe and Sibbald, 2005 [294] [pg. 69]

Information and *patient characteristics* influenced the reasons provided by families for preferences. Information was provided by recruiters (about trial interventions) and came from other sources (e.g. discussions with wider family). Additional information sources used by parents in the trials reported in this thesis included drawing on their own or a close family member's past experience of a 'nasty' appendicitis which resulted in rupture - this was a strong predictor of families declining the CONTRACT RCT. Medical history of patients, or that of a close family member have been cited as important factors in decision-making about trial participation. [280] Parents of children considering CFS/ME trials reported searching for evaluations of CFS/ME treatments online from non-NHS sources.

Patient characteristics might include length of illness, perceived level of pain, or belief that an intervention is 'better suited' to a patient's personality. The patient's evaluation of their own *self-efficacy* in relation to treatment outcomes and preference judgements is particularly relevant in trials which require adherence to a treatment protocol extending over several months. [78, 359, 360] This was an important factor in the CFS/ME trials, where some young people had negative perceptions (which may have been reinforced by parents) of their ability to engage in one of the intervention groups in the trials, e.g. group work, CBT and in particular physical activity (Graded Exercise Therapy in the MAGENTA RCT). These factors do not rely on *'expectancies'* about treatment which may be more amenable to change via balanced information about trial groups. Instead, they rely on subjective evaluations which result in preferences which may differ in strength depending on the individual or family.

The way in which *utility* is conceptualised in relation to preference is also considered as part of the preference model, with *altruism* highlighted as a potential source of utility for those considering trial participation. Parents and young people taking part in the four trials reported altruistic reasons for doing so, as previously reported in the paediatric literature when parents and young people consider trial participation. [172, 326, 671] However, altruism was discussed alongside other motivating factors, including the hope for personal benefit as well as the benefit of others in the wider community in future. This links to research literature which suggests a more accurate way of discussing altruism and research (or specifically trial) participation is by viewing it as part of a 'social exchange' where there are multiple reasons for

participating - in most instances altruism will not be the primary motivating factor. [671]

Non-utility sources of influence, such as '*coercion*', were mentioned as problematic for those recruiting to the CONTRACT RCT, although in line with research literature CONTRACT families did not highlight coercion as an issue during interviews. [96] Training for health professionals recruiting to RCTs should include ways to explore preference for treatment with families and young people in an informative and non-coercive way. Discussions between trialists and health professionals on 'patient choice', RCT participation, and access to treatment may also be useful during training sessions, particularly in RCTs which involve ongoing treatment over an extended period of time after randomisation.

The value that parents and young people placed on altruism and perceived utility of other elements of the trial, such as focusing on one intervention, (e.g. activity management in the MAGENTA trial) as opposed to combining elements of Graded Exercise Therapy *and* activity management outside the RCT (see: More is better 'pick and mix' approach) highlights the perceived 'limited' utility of RCT participation for some families. In contrast, the prospect of gaining access to an additional intervention (e.g. the Lightning Process) by participating in the SMILE RCT, highlights the way in which utility and expectancies vary considerably between trial contexts.

6.2.7 Expanding the existing model of patient preference and decision-making

A number of additional factors are pertinent when considering aspects of Bower et al's four-stage model of preference development and operation within the context of paediatric trials. [294] The 2005 model is primarily based on RCTs consenting adult participants who are making the decision to participate for themselves, with additional but limited support from a clinical team and family members. In the context of paediatric RCTs, the interaction of multiple opposing or concurring preference views is likely to have important implications for decision-making and young peoples' continued trial involvement.

Findings from my thesis research demonstrate that young people and parents frequently report different preferences for treatment, (Conflicting parent-child preference) with potential for different preferences between parents (Conflicting parent-parent preference). This was also observed in a past (surgical) paediatric RCT, [66] however young people do value shared decision-making during times of ill health. [395, 399] Further investigation is needed to determine how conflicting preferences are negotiated during the course of recruitment consultations, how they are managed or resolved during long-term RCT treatment interventions, and whether or not negotiation occurs in collaboration with treating health professionals.

My thesis research also found that preference is not static in participant or parent reports - preference for treatment can change for an individual, during the course of recruitment discussions, and/or during RCT intervention delivery. Changes in

preference have been observed in a paediatric trial investigating different modes of treatment delivery, and more generally in a review of preference effects in adult RCTs. [289, 291] The fact that preferences for treatment may change over time has implications for behavioural interventions, particularly those that require 'buy in' from the patient, parent(s) and treating health professional(s). During the course of the present thesis research some health professionals reported changes in their preference for treatment as they interacted with families and were exposed to one or more (previously unfamiliar) interventions on a more regular basis. This in turn may influence families' ongoing views and preferences. Measuring participant, parental or health professional preference before recruitment, and using this to predict and examine the effects of preference post-randomisation, may also therefore be difficult because of fluctuation and changes in preference over time.

Finally, this thesis research highlights the way in which the 2005 model should be expanded to explore parental preferences and expectancies about treatment in relation to parental self-efficacy, and specifically the way in which parents influence their child's self-efficacy. Parental self-efficacy is likely to be a very important factor in the context of paediatric RCTs, particularly those involving long term commitment to interventions for chronic health conditions. [145, 360, 658, 672] Treatment interventions for long term health conditions such as CFS/ME, obesity and diabetes nested within paediatric RCTs will include elements of self-efficacy, outcome expectancy, goal setting and behaviour change. [145, 295, 673-675] Preference judgements rely on expectancies about outcome which draw on patient evaluations of their own self-efficacy but are also likely to be informed by parent views of their own and their child's self-efficacy.

Self-efficacy must also be considered on two levels, initially at the level of successful engagement with RCT processes, (e.g. participation in research discussions and the completion of outcome measures) and successful engagement with RCT interventions (e.g. is behaviour change attainable, can I commit to one of the RCT interventions?). When young people perceived that researchers proactively engaged them by inviting their questions and opinions, young people reported greater decisional self-efficacy. [676] However, the extent to which decisional self-efficacy relates to an individual's confidence and belief in their ability to make changes to their behaviour and outcome expectancy (anticipated positive or negative consequences their actions produce) is not well understood in the context of wider health and RCTs. [677]

These are important additional factors when considering this model in the paediatric context. It is important that the views of young people and children are heard in the context of RCT research. The tendency for parents to 'dominate' research consultations when both parents and young people are present has been reported previously and was also apparent in the current findings, (see: Complexity of triadic consultations and Conflicting parent-child preferences). [96]

6.2.8 Ethical issues and participation in paediatric RCTs

The FITNET-NHS and SMILE trial were similar in that both trials offered the opportunity of access to an intervention which was potentially otherwise unavailable (the Lightning Process course was unaffordable for many, and Online CBT modules were not available outside the trial). Those eligible for both trials could access

specialist CFS/ME treatment outside the trial, (this included access to activity management, CBT and Graded Exercise Therapy) but eligible FITNET-NHS families may have had to travel a considerable distance to access this treatment. This is an important issue which should be considered carefully by recruiters exploring preferences for treatment, specifically because families may feel uncomfortable expressing their preferences if they feel treatment may be unavailable to them. An open and honest discussion of what treatment is available outside the RCT, and highlighting that trial interventions are currently both considered to be good options for eligible patients should also be discussed with care in these circumstances.

Some families still consented to randomisation and trial participation despite preference(s) for treatment, (SMILE, MAGENTA, CONTRACT & FITNET-NHS). This has been observed in adult trials. [296] This is an important finding, because when participants make decisions about randomisation which conflict with their preference for treatment, their preference may still influence their engagement with the allocated intervention in the trial. It is important to consider the existing relationship that a recruiter has with the family. If a family is presented with trial information by a health professional who has provided a diagnosis and will continue to provide ongoing care, parents (and some young people depending on their age and maturity) may feel indebted to the health professional or clinical team. The line between clinical care and research involvement may be more blurred, as compared to families who are introduced to a trial by a research nurse they have never met before and will have no involvement with ongoing clinical care. [109, 380-382]

My thesis data highlights that paediatric recruitment consultations are more complex, because there are differences in how young people and their parents communicate preference. It also highlights that young people often have different preferences for treatment from their parents. Efforts should be made to explore the preferences of young people in accordance with their current health state and ability to be involved in an informed discussion. Communication in paediatric RCTs is more complex because young people and parents all play an active role in decision-making about trial participation. It was often difficult to gauge young people's views about treatment and trial participation - this concurs with past paediatric trials research. [96] Future training for trialists and health professionals should take into consideration this additional complexity.

Voluntariness of consent, assent and access to treatment is an important issue which requires consideration in any trial context. The current findings support past research which has found that parents are more likely to respond to 'general' questions if they are not specifically directed at young people, and that young people's responses to questions directed at them were typically short. [391-393] Parents often interjected during CFS/ME recruitment consultations, with the intention of 'helping their child out' by giving their views or their perception of their child's feelings or preferences. Many young people have reported that they value shared-decision making during times of ill health, [395, 399] but more research is needed to establish ways of allowing young people to maintain autonomy. [678] Young people are at a point in their life when they are likely to want to be more independent, and

this may be particularly important in behavioural trials where treatment requires commitment to self-care interventions or activity programmes. [227, 678, 679]

A longitudinal study examining the effect of choice on recruitment to family-based drug, tobacco and alcohol prevention programs found that those able to choose their intervention did not have better outcomes than those who were randomised. [650] This study measured satisfaction with intervention programs post intervention, rather than preference for an intervention at the beginning of the study. Findings were interesting since there were differences between the satisfaction levels reported by young people and their parents, with parents being more satisfied in the 'choice' condition as opposed to 'randomised' condition. This highlights the added complexity when dealing with participation issues, preference issues prior to an intervention, and satisfaction post intervention in paediatric trials.

6.3 Strengths and limitations

6.3.1 Strengths

The findings reported in this thesis are based on a large dataset, which drew on data from four different paediatric trial settings. A large dataset is not itself important when using qualitative approaches to data analysis but is a strength in the current context since findings are not limited to one trial site, context or paediatric condition. Three CFS/ME trials were included in the data analysis. Although investigating interventions for the same condition, the three trials differed in terms of the

interventions offered in the trials and the availability of these interventions outside the trial. Families eligible for the MAGENTA and CONTRACT RCTs could easily access similar interventions outside of the trial, but for FITNET-NHS and SMILE families this was not the case.

The data collection and analysis methods used in the four paediatric trials are a strength of this research. They allowed for a comparison of themes that were identified independently in each trial context (constant comparison methods), as well as comparing and contrasting themes across trials (framework analysis). Findings were discussed with my supervision team (EC, NM and BY) as well as colleagues working in each trial team at regular intervals during the data collection and analysis processes. [550, 680]

Many qualitative research studies and those embedded in RCTs rely solely on interview data, and do not compare findings from two or more data collection methods. [461, 681] During this thesis I collected, and paired recruitment consultations and interview data, allowed for comparisons and analysis of real time recruitment practices, as well as retrospective reported practices from families and health professionals. [550] This added contextual information and allowed a more in-depth and thorough understanding of the way in which preferences were discussed at the time the decision to participate was made, as well as retrospective reflections and rationale for treatment preferences, and is considered a particular strength. [463]

This thesis research also included some analysis of issues relating to preference, retention and withdrawal from paediatric trials. The analysis of families' accounts of

the impact which preference for treatment had on their decision to discontinue treatment after several months, (MAGENTA) or requests to withdraw from treatment post-randomisation (CONTRACT) enabled an understanding of why families make such decisions in the context of each RCT. [463]

Families were interviewed at more than one time point (e.g. before or after intervention delivery), therefore findings were not limited to one point in the trial process. Conducting interviews on three occasions during the SMILE RCT (before, after randomisation, and after the intervention) helped to facilitate rapport with families and highlighted the way in which preference for treatment may change over time. Although this approach was not used in the MAGENTA and FITNET-NHS trials (and was not feasible in an acute care setting), it demonstrates that the timing of qualitative research may be an important factor when investigating preference for treatment, specifically if the research team wish to gain families' perspectives before they have made the decision to participate in an RCT.

Participating health professionals delivered a range of interventions, in complex paediatric RCTs in acute and chronic care settings. Members of wider clinical teams were interviewed (e.g. those delivering ongoing care after randomisation) as well as those recruiting to the trials. Interviews also included a range of health professionals, including research nurses and those from a variety of specialties (occupational health, physiotherapy, surgery, psychology and specialist paediatric consultants) in the wider multidisciplinary team.

The large data sample also reflects the fact that a high number of recruitment consultations were routinely recorded in each of the four RCTs, which demonstrates that recruiters were willing to record these interactions and allowed for the analysis of a wide range of consultations with varied outcomes (e.g. families who consented to and declined each RCT). Some recruiters initially felt uneasy about making recordings of recruitment consultations. However, high numbers of consultations were recorded in each trial, recruiters were engaged with the research team, reported that the training sessions were useful, and reported that the communication techniques discussed could be put into practice in future consultations. Analysis of recruitment consultations before and after training also allowed for a comparison of changes in dealing with preferences among other aspects of practice, and the way in which this impacted recruitment figures.

Fathers were purposively sampled during the MAGENTA, FITNET-NHS and CONTRACT trials. The inclusion of fathers' experiences and input in the decision-making process is considered a strength of the current thesis findings. The research literature has often focused on mothers' views and experiences (because mothers are often the primary carer). [108, 120, 204, 316, 507, 524] However fathers and other close family members also play an important role in decision-making when trial participation is considered for a child. [682-684]

6.3.2 Limitations

Interviews

The preference data collected from interviews for this thesis was limited by the overall aims of the four main collaborating trials. Data collection for each trial focussed not only on preference for treatment (the focus of this thesis), each trial also collected more general data on a number of other feasibility issues explored by each nested qualitative study. Topic guides used in each trial contained a limited number of questions on preference for treatment as questions relating to all areas of trial feasibility had to be covered, thus time spent discussing preference in interviews was limited. As a result, preference data collected via interview was not as in-depth as it might have been had each interview solely focused on preference issues.

Asking participants to think ‘retrospectively’ about preference for treatment may have influenced participants to feel they ‘should’ have had, or were being asked to ‘construct’ preferences for treatment. Retrospective views about preference will be affected by the experience and satisfaction of young people and their parents with the intervention they received as part of the RCT, thus by asking questions about trial participation more generally expressions of strongly held views on preference could be and were raised by families and health professionals while discussing other trial concepts (e.g. trial rationale and randomisation).

It was not always possible to interview recruiters soon after specific recruitment consultations (where families had discussed preferences for treatment or declined the trial). Recruiters did not always remember the detail of consultations if they had taken place a number of weeks prior to the interview. Conversations about preference were often part of wider discussions about treatment and recruitment, therefore recruiters were usually only able to discuss specific ‘preference’ related aspects of consultations if they had taken place immediately before the interview. One advantage of a delayed interview was that thorough analysis of the related recruitment consultation could be carried out prior to interview. Preference related issues could then be raised by the interviewer and potentially discussed in more detail by the interviewee.

Beliefs expressed at interview are co-constructed between the interviewer and the interviewee. Those conducting interviews across the four trials had varied levels of experience in the field of qualitative research interviewing, and this may have had an impact on the quality of the data collected. [685] Those with limited experience of qualitative interviewing asked more closed questions, and at times failed to use probing questions to explore treatment preferences. Feedback from those with more limited experience of collecting qualitative data highlighted worries about ‘changing the wording of questions’ and ‘not fitting all the questions into the interview’.

Although telephone interviews may be convenient and less intrusive for both the interviewee and interviewer there is a loss of contextual information such as visual

cues - particularly useful when interviewing those with CFS/ME who may feel tired as the discussion progresses. Other information about the neighbourhood in which a family live and their homelife is also more apparent during face-to-face interviews in the participant's home. Some young people were difficult to engage in telephone conversations, and face-to-face interviews tended to be more productive in terms of building rapport and gaining rich in-depth information.

It was more difficult to arrange interviews with families who had declined the trials, despite these families indicating that they were happy to be contacted by a researcher - some did not respond to messages or cancelled interviews which had been arranged. During the CONTRACT trial some parents did not ask their child if they wished to participate in an interview because they might either not remember details of the trial because they were too ill, or they felt it was inappropriate and might make their child reflect upon distressing memories of being particularly unwell.

Recruiters and health professionals were not routinely interviewed during recruitment to the SMILE RCT - this aspect of QRI methodology was developed after ethical approval for the trial had been obtained. It became clear after qualitative work was completed in the SMILE trial that feedback from recruiting health professionals and members of the wider CFS/ME team would have been useful, therefore this was implemented in future paediatric trials (MAGENTA, FITNET-NHS and CONTRACT).

Methodology and analysis

Recruiters' ability to constructively cede the floor and allow young people to contribute to recruitment consultations may have been exacerbated during recruitment to MAGENTA and FITNET-NHS as these consultations were conducted via telephone. Recruiters did not have the visual cues to anticipate whether individuals wanted more time to respond, at times relying on parent reports to determine young people's feelings about treatment preference, e.g. "*He's screwing his face up*". Recruiters were advised to use a young person's name to direct specific questions so that parents did not dominate conversations, but in a small number of conversations it became apparent that young people had 'left the room to use the toilet' and were not fully engaged with the conversation.

Grounded theory works on the principle of an iterative analysis allowing for the testing of emerging theory. The fast-paced context of each RCT feasibility study did not always allow for extensive in-depth iterative analysis, and proved particularly difficult when analysing themes between the four RCTs. Framework analysis was used to manage and compare data due to the availability of a large amount of data across four different trials. However, this inevitably resulted in a loss of the iterative testing of findings and themes, which were relevant across and between the four trials but were identified too late to be 'tested' in the individual trial populations.

It is important to recognise that my knowledge of the subject area and data analysis from the SMILE and MAGENTA trials may have affected later data collection and

analysis in the CONTRACT and FITNET-NHS trials. [458] Analysing data from three CFS/ME trials means that these findings are not as broad as they would be if collaborations had been formed with trials in four different paediatric areas, e.g. a vaccination trial with a ‘well’ paediatric population, or a diabetes trial. Using content analysis to analyse ‘expressed’ preference allowed only for the aggregation of preference, it did not highlight important contextual factors such as availability of treatment outside of the RCT, and it was therefore not used to analyse recruitment consultation data from MAGENTA, FITNET-NHS or CONTRACT.

6.4 Recommendations and implications for future research

The current research findings improve RCT conduct and methodology in paediatric trials by highlighting issues of importance to families and health professionals during recruitment and participation in paediatric trials. These findings have already contributed to preliminary guidance documents for health professionals recruiting to paediatric trials, outlining strategies to identify and discuss treatment preference and equipoise in partnership with young people and their parents (see: Appendices 4, 5 and 6: tips for recruitment, and Appendix 6: CONTRACT: Recruitment Flowchart). The CONTRACT trial recruited young people who had an unscheduled hospital admission, which is a setting where recruitment to research can be particularly challenging due to time limitations, the demanding clinical environment and the heightened stress levels of parents and young people. A recent systematic review

highlighted the lack of high-quality research investigating recruitment processes in RCTs which involved unplanned hospital admission, and the need for high quality verbal rather than written information in this trial context. [686] Further research in this area is required, particularly in RCTs where recruitment strategies or training programs are also randomised, in order to compare their effectiveness. [687]

Future research based on Bower's conceptual model could include an investigation of 'global preference' and the weighting given by young people and their parents to utility components of the model. These might include utility from participating (e.g. altruism and social exchange), availability of treatments outside the trial, and the probability of receiving a specific intervention in the trial. Exploration of these components of preference in a trial (with training for recruiters) might lead to a model of 'informed expectancies' specific to families' decision-making on trial participation. Self-efficacy may hold more weight in complex trials requiring behavioural modification and commitment from participants over an extended period. The effect of self-efficacy on retention in behavioural trials is an area which requires further investigation. [688] Preference cannot be viewed as static - those who are initially disappointed when randomised to their non-preferred intervention group may later find the approach useful and effective. Thus, the measurement of preference before recruitment and its use to predict and examine the effect on retention may be unreliable. This thesis has found altruism or social exchange to be an important utility. It would also be important to consider potential benefit (faster recovery) and risk (treatment side effects) in relation to trial utility and preference for treatment. The investigation of why young people and parents with a preference for treatment

consent to a trial when they are able to access the treatment externally is also important to consider when families make decisions about trial participation.

A high proportion of conversations forming ‘part’ of recruitment consultations were not recorded during the CONTRACT RCT. This included initial conversations where the trial was introduced and final conversations where group allocation was given verbally to families. Although the research team routinely asked that all conversations about the trial be recorded, particularly those where families were given their group allocation, since parent or patient responses might display disappointment or excitement about the allocated intervention group. Recruiters either did not see the utility of recording these conversations, or felt unable practically and logistically to record them.

Future research might look at innovative ways in which this type of information could be captured and used for research purposes with consent from families. This might include video recording the initial assessment appointment and would enable researchers to use conversation analysis to investigate specific sections of consultations where preference is discussed. The availability of visual as well as audio cues would enable a more in-depth analysis of the way in which families, recruiters or health professionals express or respond to preference, and possibly present a position of equipoise. These additional ‘mini’ consultations between health professionals and families prior to the ‘main’ recruitment consultation are likely to be important in terms of preference formation. It is not clear whether personal opinion and recommendations were apparent during these unrecorded conversations (see:

Missing conversations from the consultation process). ‘Preference’ related data may have been lost from conversations which occurred before the main recruitment consultations, e.g. during the first FITNET-NHS phone call, or the eligibility assessment and initial clinical appointments in the SMILE and MAGENTA trials. The potential for communication about a trial to occur at multiple consultations has been noted in previous research in a paediatric setting, and more widely in research investigating decision-making in health care settings. [109, 689]

A recent paper (2016) investigating parental reasons for declining participation in paediatric surgical trials found that the most common reason for doing so was preference for treatment (37%). [690] The authors state that better communication and explanation of trial rationale and treatment might be an effective way to tackle this issue. It is recommended that conversations to clarify and outline trial rationale should begin as early as possible in the consultation process, for example at the outpatient clinic stage for elective surgery, as early conversations may be key to the formation of preference for treatment. This indicates the importance of all conversations taking place between health professionals at all stages of the trial recruitment consultation process (see: Missing conversations from the consultation process). However, further research is required to determine the feasibility of making additional records of these conversations, particularly in an acute care setting where recorders may be stored securely in another area of the hospital.

The effect of preference for treatment on the responses of young people and their parents to returning primary outcome measures as part of each ongoing RCT was

not investigated in this thesis. This is important when considering satisfaction with treatment (particularly in behavioural trials), and the impact that treatment preference and/or satisfaction with treatment might have on missing data. The interaction between preference for treatment at trial outset and satisfaction with ongoing treatment as a trial progresses also requires further investigation. Further in-depth analysis of the complexity of paediatric trial consultations is needed, to understand the way in which the views and preferences of young people under the age of 16 are considered. Conversation analysis could be used to examine and explore turn-taking behaviour in paediatric recruitment consultations, particularly where both parents are present and participate in the decision-making process in collaboration with their child.

Future research should explore the concepts of personal and collective equipoise with health professionals recruiting to trials, and those working with and treating young people post-randomisation. Pre-trial training should consider how health professionals view taking on the dual roles of clinician and recruiter. Issues relating to intervention groups and equipoise could be discussed by the teams who will be required to recruit to trials. It may also be important to consider treatment equipoise in place of treatment preference when developing future training and discussing trial rationale in partnership with families and health professionals. Rather than focusing on preference for treatment this training might focus instead on equipoise and treatment, thus exploring the way in which recruiters and wider team members view treatment conceptually as well as its practical delivery.

The way in which research teams and NHS clinical teams work together collaboratively could be improved using an ‘action learning’ and ‘action research’ approach so that all involved have an investment in the way in which data is collected and used. Pre-trial consultation meetings with clinical teams to discuss eligibility criteria and views on treatments should be investigated in future trials. The meetings should be audio-recorded where possible. Before trials commence interviews or focus groups with recruiters and wider teams delivering the interventions or care should be held. This will help to better understand team ‘mood’. These measures, and the continued inclusion of patient groups and their feedback are crucial to the acceptability of trial interventions during the planning and implementation phase of trials.

Observed improvements in communication after training, and the effect of this on recruitment in different trial contexts is worthy of continued research and consideration. Although recruitment did not increase month on month, there appeared to be a ‘training effect’ in the three trials which used more structured forms of training for recruiters. Further research is needed in order to understand the ‘active ingredient’, or way in which training influences recruitment, and how this training might be extended to wider clinical teams coming into contact with those considering trial participation or participating in continued clinical care as part of a trial.

Greater transparency and consistency in the way in which recruitment processes are reported in published papers is required, particularly in terms of patient flow prior to

eligibility. Paediatric RCTs might benefit from using the SEAR framework to track the number of families: *Screened, Eligible, Approached and Randomised*. [417] Generalised phrases used to record reasons for non-participation e.g. 'does not want to take part in research' could be either a reflection on wider perceptions of research, or specific to one or more of the RCT interventions. Reason codes which are highly prescriptive particularly during the feasibility or internal pilot stage of a trial will not provide clinical teams or trialists with a clear view of the reasons why families decline a trial. For example in CONTRACT only two reason codes were used for those who declined the trial.

6.5 Conclusions

This thesis provides an increased understanding of treatment preference in paediatric RCTs. It has made a unique contribution in four areas: a) identifying that young people have treatment preferences, b) that young people and their families continue to consent to trials despite having preferences, c) that discussions of preference during recruitment can occur at any time, and d) that recruitment communication training can contribute to successful recruitment during feasibility and internal pilot paediatric RCTs.

a) Preference for treatment is an important issue that should be explored when recruiting to paediatric trials which deliver complex behavioural or surgical interventions. This thesis has shown that young people and parents have treatment preferences which influence recruitment to paediatric RCTs. The reporting of young

peoples' preferences for treatment has not been prominent in past literature. The emotional and complex nature of preference discussions has also been identified: for parents wanting the best for their child; young people wanting to get better and help others; and health professionals balancing individual versus collective equipoise.

b) Despite expressing preferences for treatment many families make the decision to participate in paediatric RCTs, therefore open discussions about preference are an important part of the informed consent process. This may be more prominent for RCTs delivering one or more interventions not available outside the RCT and could have further implications for retention and the completion of outcome measures. This is particularly relevant if trial interventions are ongoing over a prolonged period of time e.g. behavioural interventions.

c) This thesis also identified that preference for treatment can arise in a number of different discussions between recruiters and families, not only during discussions specifically about the treatments offered in an RCT or discussions which occur immediately prior to consent. Preference for treatment can arise in discussions about trial processes, when families are discussing treatment, and post randomisation.

d) Training recruiters to reflect on how they convey trial information improves communication about trial rationale, the exploration of treatment preferences, and discussions of equipoise between intervention groups. Training also appears to have a positive effect on recruitment, although the mechanisms of this remain unclear.

The views and equipoise of those recruiting and treating RCT intervention participants influenced families at all stages of recruitment and intervention delivery and are likely to be an important influence on recruitment and retention as an RCT progresses.

Further research is needed in paediatric settings to investigate the way in which health professionals discuss treatment options before and after the main recruitment consultation, including more transparency in relation to the way in which reasons for trial decline and discontinuation of interventions are sought and recorded. Future research should investigate the way in which a lack of health professional or family equipoise impacts retention in paediatric RCTs.

References

1. General Medical Council, *0–18 years: guidance for all doctors. Working with doctors. Working for patients*. 2018, The GMC is a charity registered in England and Wales (1089278) and Scotland (SC037750).
2. Cochrane. */glossary#letter-R*. 2018; Available from: http://community.cochrane.org Accessed 10/05/2018.
3. Howick, J. *Oxford Centre for Evidence-based Medicine – Levels of Evidence*. 2009 Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes: November 1998. ; Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
4. Evans, D., *Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions.* J Clin Nurs, 2003. **12**(1): p. 77-84.
5. Muir Gray, J.A., et al., *Transferring evidence from research into practice: 3. Developing evidence-based clinical policy.* ACP J Club, 1997. **126**(2): p. A14-6.
6. Sackett, D.L., *Evidence-based medicine and treatment choices.* Lancet, 1997. **349**(9051): p. 570; author reply 572-3.
7. Patsopoulos, N.A., A.A. Analatos, and J. Ioannidis, *Relative citation impact of various study designs in the health sciences.* JAMA, 2005. **293**(19): p. 2362-6.
8. Cochrane, *Handbook for Systematic Reviews of Interventions*, T.C. Collaboration, Editor. 2011.
9. Singal, A.G., P.D.R. Higgins, and A.K. Waljee, *A Primer on Effectiveness and Efficacy Trials.* Clinical and Translational Gastroenterology, 2014. **5**(1): p. e45.
10. Schwartz, D. and J. Lellouch, *Explanatory and pragmatic attitudes in therapeutical trials.* J Chronic Dis, 1967. **20**(8): p. 637-48.
11. Thorpe, K.E., et al., *A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers.* CMAJ, 2009. **180**(10): p. E47-57.
12. Sackett, D.L. and W.M. Rosenberg, *The need for evidence-based medicine.* J R Soc Med, 1995. **88**(11): p. 620-4.
13. British Broadcasting Corporation (BBC). *The NHS: 'One of the greatest achievements in history'* 1998 May 2018].
14. Department of Health, *The health of the nation: a strategy for health in England*. 1992, HMSO: London.
15. Gabbay, J., *The health of the nation.* British Medical Journal, 1992. **305**(6846): p. 129-130.
16. Hanney, S., et al., *An assessment of the impact of NHS* Health Technology Assessment Programme. Health Technol Assess 2007. **11**(53).
17. Department of Health, *Assessing the Effects of Health Technologies: Principles, Practice, Proposals.* 1992, London: Great Britain: NHS Management Executive: Advisory Group on Health Technology Assessment.
18. NICE: National Institute for Health and Clinical Excellence. *History of NICE*. 2018 May 2018].
19. European Commission, *The Medicines for Human Use (Clinical Trials) Amendment Regulations*, in *No. 1928 Medicines Statutory Instruments*. 2006.

20. Lehmann, B., *Regulation (EC) No 1901/2006 on medicinal products for paediatric use & clinical research in vulnerable populations.* Child Adolesc Psychiatry Ment Health, 2008. **2**(1): p. 37.
21. Donaldson, I.M.L. *Ambroise Paré's accounts of new methods for treating gunshot wounds and burns. JLL Bulletin: Commentaries on the history of treatment evaluation* 2004; Available from: http://www.jameslindlibrary.org/articles/ambroise-pares-accounts-of-new-methods-for-treating-gunshot-wounds-and-burns/.
22. Donaldson, I.M.L., *Van Helmont's proposal for a randomised comparison of treating fevers with or without bloodletting and purging. .* JLL Bulletin: Commentaries on the history of treatment evaluation 2016.
23. Lind, J., *Nutrition classics. A treatise of the scurvy by James Lind, MDCCLIII.* Nutr Rev, 1983. **41**(5): p. 155-7.
24. Science Museum. *Brought to Life: Exploring the History of Medicine*. 2017 [cited 2017 06/04/17].
25. Hrobjartsson, A., P.C. Gotzsche, and C. Gluud, *The controlled clinical trial turns 100 years: Fibiger's trial of serum treatment of diphtheria.* BMJ, 1998. **317**(7167): p. 1243-5.
26. Hopkins, W.A., *Patulin in the common cold. IV: Biological properties: extended trial in the common cold. .* Lancet 1943. **2:**: p. 631-635.
27. Stuart-Harris, C.H., A.E. Francis, and J.M. Stansfeld, *Patulin in the common cold. .* Lancet 1943. **2:**: p. 684.
28. Clarke, M. *The 1944 patulin trial of the British Medical Research Council: an example of how concerted common purpose can get reliable answers to important questions very quickly. JLL Bulletin: Commentaries on the history of treatment evaluation* 2004; Available from: http://www.jameslindlibrary.org/articles/the-1944-patulin-trial-of-the-british-medical-research-council-an-example-of-how-concerted-common-purpose-can-get-reliable-answers-to-important-questions-very-quickly/.
29. Medical Research Council, *STREPTOMYCIN treatment of pulmonary tuberculosis.* Br Med J, 1948. **2**(4582): p. 769-82.
30. Crofton, J., *The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line.* J R Soc Med, 2006. **99**(10): p. 531-4.
31. Hill, A.B., *Medical ethics and controlled trials.* Br Med J, 1963. **1**(5337): p. 1043-9.
32. *Antibiotic Combinations.* 1956. **255**(22): p. 1057-1059.
33. Haarsager, J., *Podolsky, S.H. The Antibiotic Era: Reform, Resistance, and the Pursuit of a Rational Therapeutics. Baltimore: Johns Hopkins University Press. 2015. 328 pp $34.95 ISBN 978-1-4214-1593-2.* 2015. **37**(8): p. 1391-1392.
34. Shen, W.W., *A history of antipsychotic drug development.* Compr Psychiatry, 1999. **40**(6): p. 407-14.
35. Greene, J.A. and S.H. Podolsky, *Reform, regulation, and pharmaceuticals--the Kefauver-Harris Amendments at 50.* The New England journal of medicine, 2012. **367**(16): p. 1481-1483.
36. National Institute for Biological Standards and Control (NIBSC). 1972 [cited 2018 10/08/2018].
37. Medicines & Healthcare products Regulatory Agency (MHRA). *Clinical trials for medicines: apply for authorisation in the UK*. 2003 [cited 2018 10/08/2018].

38. Bothwell, L.E., et al., *Assessing the Gold Standard--Lessons from the History of RCTs.* N Engl J Med, 2016. **374**(22): p. 2175-81.
39. Jones, D.S. and S.H. Podolsky, *The history and fate of the gold standard.* The Lancet, 2015. **385**(9977): p. 1502-1503.
40. Lurie, P. and S.M. Wolfe, *Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries.* N Engl J Med, 1997. **337**(12): p. 853-6.
41. Rothman, D.J., *The shame of medical research.* New York Rev Books, 2000. **47**(19): p. 60-4.
42. Burdett, S., L.A. Stewart, and J.F. Tierney, *Publication bias and meta-analyses: a practical example.* Int J Technol Assess Health Care, 2003. **19**(1): p. 129-34.
43. Zarin, D.A., et al., *Issues in the registration of clinical trials.* JAMA, 2007. **297**(19): p. 2112-20.
44. Nuffield Council on Bioethics, *Children and clinical research: ethical issues*. 2015, Nuffield Council on Bioethics: London ESP Colour Ltd.
45. Deatrick, J.A., D.B. Angst, and C. Moore, *Parents' views of their children's participation in phase I oncology clinical trials.* J Pediatr Oncol Nurs, 2002. **19**(4): p. 114-21.
46. Arain, M., et al., *What is a pilot or feasibility study? A review of current practice and editorial policy.* BMC Med Res Methodol, 2010. **10**: p. 67.
47. Eldridge, S.M., et al., *Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework.* PLoS One, 2016. **11**(3): p. e0150205.
48. Avery, K.N., et al., *Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies.* BMJ Open, 2017. **7**(2): p. e013537.
49. Guyatt, G.H., et al., *A clinician's guide for conducting randomized trials in individual patients.* CMAJ, 1988. **139**(6): p. 497-503.
50. Guyatt, G.H., et al., *The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience.* Ann Intern Med, 1990. **112**(4): p. 293-9.
51. Duan, N., R.L. Kravitz, and C.H. Schmid, *Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness research.* J Clin Epidemiol, 2013. **66**(8 Suppl): p. S21-8.
52. Lillie, E.O., et al., *The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?* Per Med, 2011. **8**(2): p. 161-173.
53. Sung, L. and B.M. Feldman, *N-of-1 trials: innovative methods to evaluate complementary and alternative medicines in pediatric cancer.* J Pediatr Hematol Oncol, 2006. **28**(4): p. 263-6.
54. Nikles, C.J., A.M. Clavarino, and C.B. Del Mar, *Using n-of-1 trials as a clinical tool to improve prescribing.* Br J Gen Pract, 2005. **55**(512): p. 175-80.
55. Cook, D.J., *Randomized trials in single subjects: the N of 1 study.* Psychopharmacol Bull, 1996. **32**(3): p. 363-7.
56. Gallin, J.I. and F.P. Ognibene, *Principles and Practice of Clinical Research* Vol. (Third Edition). 2012: Academic Press is an Imprint of Elsevier.
57. McNamara, D.G., A.R. Dickinson, and C.A. Byrnes, *The perceptions and preferences of parents of children with tracheostomies in a study of humidification therapy.* J Child Health Care, 2009. **13**(3): p. 179-97.
58. Brewin, C.R. and C. Bradley, *Patient preferences and randomised clinical trials.* BMJ, 1989. **299**(6694): p. 313-5.

59. Olschewski, M., M. Schumacher, and K.B. Davis, *Analysis of randomized and nonrandomized patients in clinical trials using the comprehensive cohort follow-up study design.* Control Clin Trials, 1992. **13**(3): p. 226-39.
60. Howard, L. and G. Thornicroft, *Patient preference randomised controlled trials in mental health research.* Br J Psychiatry, 2006. **188**: p. 303-4.
61. Relton, C., et al., *Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design.* BMJ, 2010. **340**: p. c1066.
62. Torgerson, D.J., J. Klaber-Moffett, and I.T. Russell, *Patient preferences in randomised trials: threat or opportunity?* J Health Serv Res Policy, 1996. **1**(4): p. 194-7.
63. Britton, A., et al., *Choosing between randomised and non-randomised studies: a systematic review.* Health Technol Assess, 1998. **2**(13): p. i-iv, 1-124.
64. Silverman, W.A. and D.G. Altman, *Patients' preferences and randomised trials.* Lancet, 1996. **347**(8995): p. 171-4.
65. Bond, J., et al., *Protocol for north of England and Scotland study of tonsillectomy and adeno-tonsillectomy in children (NESSTAC). A pragmatic randomised controlled trial comparing surgical intervention with conventional medical treatment in children with recurrent sore throats.* BMC Ear Nose Throat Disord, 2006. **6**: p. 13.
66. Lock, C., et al., *North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children(NESSTAC): a pragmatic randomised controlled trial with a parallel non-randomised preference study.* Health Technol Assess, 2010. **14**(13): p. 1-164, iii-iv.
67. Torgerson, D.J. and B. Sibbald, *Understanding controlled trials. What is a patient preference trial?* BMJ, 1998. **316**(7128): p. 360.
68. Cooper, K.G., A.M. Grant, and A.M. Garratt, *The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding.* Br J Obstet Gynaecol, 1997. **104**(12): p. 1367-73.
69. Klein, S., et al., *Evaluating the effectiveness of a web-based intervention to promote mental wellbeing in women and partners following miscarriage, using a modified patient preference trial design: an external pilot.* BJOG, 2012. **119**(6): p. 762-7.
70. Zelen, M., *Alternatives to classic randomized trials.* Surg Clin North Am, 1981. **61**(6): p. 1425-32.
71. Chang, R.W., et al., *Prerandomization: an alternative to classic randomization. The effects on recruitment in a controlled trial of arthroscopy for osteoarthrosis of the knee.* J Bone Joint Surg Am, 1990. **72**(10): p. 1451-5.
72. Snowdon, C., D. Elbourne, and J. Garcia, *Zelen randomization: attitudes of parents participating in a neonatal clinical trial.* Control Clin Trials, 1999. **20**(2): p. 149-71.
73. O'Rourke, P.P., et al., *Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study.* Pediatrics, 1989. **84**(6): p. 957-63.
74. Snowdon, C., J. Garcia, and D. Elbourne, *Making sense of randomization; responses of parents of critically ill babies to random allocation of treatment in a clinical trial.* Soc Sci Med, 1997. **45**(9): p. 1337-55.

75. Schulz, K.F. and D.A. Grimes, *Generation of allocation sequences in randomised trials: chance, not choice.* Lancet, 2002. **359**(9305): p. 515-9.
76. Schulz, K.F. and D.A. Grimes, *Blinding in randomised trials: hiding who got what.* Lancet, 2002. **359**(9307): p. 696-700.
77. Yang, H., et al., *Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication: 10-year outcomes.* Ann Surg, 2008. **247**(1): p. 38-42.
78. Crawley, E., et al., *Comparing specialist medical care with specialist medical care plus the Lightning Process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial).* Trials, 2013. **14**: p. 444.
79. Higgins, J.P.T., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* BMJ, 2011. **343**.
80. Treweek, S., et al., *Strategies to improve recruitment to randomised trials.* Cochrane Database Syst Rev, 2018. **2**: p. MR000013.
81. Hemminki, E., et al., *Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy.* J Clin Epidemiol, 2004. **57**(12): p. 1237-43.
82. Avenell, A., et al., *The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design.* Clin Trials, 2004. **1**(6): p. 490-8.
83. Powell, J.T., et al., *Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial.* Br J Surg, 2007. **94**(6): p. 702-8.
84. Cook, J.A., *The challenges faced in the design, conduct and analysis of surgical randomised controlled trials.* Trials, 2009. **10**(1): p. 9.
85. McCulloch, P., et al., *Randomised trials in surgery: problems and possible solutions.* BMJ, 2002. **324**(7351): p. 1448-51.
86. Devereaux, P.J., et al., *Need for expertise based randomised controlled trials.* BMJ, 2005. **330**(7482): p. 88.
87. Devereaux, P.J., et al., *Participating surgeons' experience with and beliefs in the procedures evaluated in a randomized controlled trial.* Clin Trials, 2004. **1**(225).
88. Karanicolas, P.J., F. Farrokhyar, and M. Bhandari, *Blinding: Who, what, when, why, how?* Canadian Journal of Surgery, 2010. **53**(5): p. 345-348.
89. Blencowe, N.S., et al., *Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials.* Br J Surg, 2016. **103**(10): p. 1377-84.
90. Bowen, J. and S. Hirsch, *Recruitment rates and factors affecting recruitment for a clinical trial of a putative anti-psychotic agent in the treatment of acute schizophrenia.* Hum. Psychopharmacol. Clin. Exp., 1992. **7**: p. 337–341.
91. Kaur, G., R.L. Smyth, and P. Williamson, *Developing a survey of barriers and facilitators to recruitment in randomized controlled trials.* Trials, 2012. **13**: p. 218.
92. Kaur, G., et al., *A survey of facilitators and barriers to recruitment to the MAGNETIC trial.* Trials, 2016. **17**(1): p. 607.
93. Rothmier, J.D., M.V. Lasley, and G.G. Shapiro, *Factors Influencing Parental Consent in Pediatric Clinical Research.* Pediatrics, 2003. **111**(5): p. 1037-1041.

94. Sammons, H.M., et al., *What motivates British parents to consent for research? A questionnaire study.* BMC Pediatr, 2007. **7**: p. 12.
95. Peay, H.L., et al., *Barriers and facilitators to clinical trial participation among parents of children with pediatric neuromuscular disorders.* Clin Trials, 2018: p. 1740774517751118.
96. Shilling, V., et al., *Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study.* Health technology assessment (Winchester, England), 2011. **15**(15): p. 1-116.
97. Caldwell, P.H., P.N. Butow, and J.C. Craig, *Parents' attitudes to children's participation in randomized controlled trials.* J Pediatr, 2003. **142**(5): p. 554-9.
98. Donovan, J., et al., *Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.* Health Technol.Assess, 2003. **7**(14): p. 1-88.
99. Fernandez, C.V., et al., *Barriers to the enrollment of children in the Children's Oncology Group study of very low risk Wilms tumor: a report from the Children's Oncology Group.* J Pediatr Hematol Oncol, 2011. **33**(7): p. 521-3.
100. Hemming, K., et al., *The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting.* BMJ, 2015. **350**: p. h391.
101. Berry, S.M., J.T. Connor, and R.J. Lewis, *The platform trial: an efficient strategy for evaluating multiple treatments.* JAMA, 2015. **313**(16): p. 1619-20.
102. Hill, A.B., *The clinical trial.* N Engl J Med, 1952. **247**(4): p. 113-9.
103. Nabulsi, M., Y. Khalil, and J. Makhoul, *Parental attitudes towards and perceptions of their children's participation in clinical research: a developing-country perspective.* Journal of medical ethics, 2011. **37**(7): p. 420-3.
104. Kupst, M.J., et al., *Clinical trials in pediatric cancer: parental perspectives on informed consent.* J Pediatr Hematol Oncol, 2003. **25**(10): p. 787-90.
105. Kodish, E., et al., *Communication of randomization in childhood leukemia trials.* JAMA, 2004. **291**(4): p. 470-5.
106. Greenley, R.N., et al., *Stability of parental understanding of random assignment in childhood leukemia trials: an empirical examination of informed consent.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2006. **24**(6): p. 891-7.
107. Woolfall, K., et al., *Parents' agendas in paediatric clinical trial recruitment are different from researchers' and often remain unvoiced: a qualitative study.* PLoS One, 2013. **8**(7): p. e67352.
108. Eiser, C., et al., *Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children.* Child Care Health Dev, 2005. **31**(5): p. 517-23.
109. Byrne-Davis, L.M., et al., *Balancing high accrual and ethical recruitment in paediatric oncology: a qualitative study of the 'look and feel' of clinical trial discussions.* BMC medical research methodology, 2010. **10**: p. 101.
110. Harvey, M., et al., *'We knew it was a totally at random thing': parents' experiences of being part of a neonatal trial.* Trials, 2017. **18**(1): p. 361.
111. Wiley, F.M., et al., *Parents' perceptions of randomization in pediatric clinical trials. Children Cancer Group.* Cancer Pract, 1999. **7**(5): p. 248-56.
112. Vemulakonda, V.M. and J. Jones, *Barriers to participation in surgical randomized controlled trials in pediatric urology: A qualitative study of key stakeholder perspectives.* J Pediatr Urol, 2016. **12**(3): p. 180.e1-7.
113. Shilling, V. and B. Young, *How do parents experience being asked to enter a child in a randomised controlled trial?* BMC Med Ethics, 2009. **10**: p. 1.

114. Ward, F.R., *Chaos, vulnerability and control: parental beliefs about neonatal clinical trials.* J Perinatol, 2009. **29**(2): p. 156-62.
115. Glogowska, M., et al., *Randomised controlled trial of community based speech and language therapy in preschool children.* BMJ, 2000. **321**(7266): p. 923-6.
116. Fried, E., *The therapeutic misconception, beneficence, and respect.* Account Res, 2001. **8**(4): p. 331-48.
117. Chappuy, H., et al., *Children's views on their involvement in clinical research.* Pediatric blood & cancer, 2008. **50**(5): p. 1043-6.
118. Dolan, L.A., et al., *Preference assessment of recruitment into a randomized trial for adolescent idiopathic scoliosis.* J Bone Joint Surg Am, 2008. **90**(12): p. 2594-605.
119. Angiolillo, A.L., et al., *Staged informed consent for a randomized clinical trial in childhood leukemia: impact on the consent process.* Pediatr Blood Cancer, 2004. **42**(5): p. 433-7.
120. Carvalho, A.A. and L.R. Costa, *Mothers' perceptions of their child's enrollment in a randomized clinical trial: poor understanding, vulnerability and contradictory feelings.* BMC Med Ethics, 2013. **14**: p. 52.
121. Shilling, V., et al., *Communication about children's clinical trials as observed and experienced: qualitative study of parents and practitioners.* PLoS One, 2011. **6**(7): p. e21604.
122. Caldwell, P.H., P.N. Butow, and J.C. Craig, *Pediatricians' attitudes toward randomized controlled trials involving children.* J Pediatr, 2002. **141**(6): p. 798-803.
123. Donovan, J., et al., *Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult.* BMJ, 2002. **325**(7367): p. 766-770.
124. Paramasivan, S., et al., *Key issues in recruitment to randomised controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial (CRUK/07/011).* Trials, 2011. **12**: p. 78.
125. Mills, N., et al., *Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study.* Control Clin Trials, 2003. **24**(3): p. 272-82.
126. Jepson, M., et al., *An observational study showed that explaining randomization using gambling-related metaphors and computer-agency descriptions impeded randomized clinical trial recruitment.* J Clin Epidemiol, 2018. **99**: p. 75-83.
127. Jepson, M., et al., *"It's what we call a randomised control trial" exploring how randomisation is presented by recruiters in RCTs.* Trials, 2015. **16**((Suppl 2):O36).
128. Wilson, J.T., *An update on the therapeutic orphan.* Pediatrics, 1999. **104**(3 Pt 2): p. 585-90.
129. Cohen, E., et al., *An absence of pediatric randomized controlled trials in general medical journals, 1985-2004.* J Clin Epidemiol, 2007. **60**(2): p. 118-23.
130. Pritchard-Jones, K. and S. Europe, *Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe.*

European journal of cancer (Oxford, England : 1990), 2008. **44**(15): p. 2106-11.
131. Cohen, E., et al., *Child vs adult randomized controlled trials in specialist journals: a citation analysis of trends, 1985-2005.* Arch Pediatr Adolesc Med, 2010. **164**(3): p. 283-8.
132. Barst, R.J., *Children deserve the same rights we do: the need for paediatric pulmonary arterial hypertension clinical drug development.* Heart, 2010. **96**(17): p. 1337-8.
133. Chalmers, I., et al., *Key Concepts for Informed Health Choices: a framework for helping people learn how to assess treatment claims and make informed choices.* BMJ Evidence-Based Medicine, 2018. **23**(1): p. 29-33.
134. Nuffield Council on Bioethics. *Medicines research with children: Council welcomes EMA class waiver review*. 2015 10/05/20018]; Available from: http://nuffieldbioethics.org/news/2015/promoting-medicines-research-children-council-welcomes-emas-review.
135. Wright, K. *The Paediatric Regulation – a work in progress?* 2016 10/05/18]; Available from: http://nuffieldbioethics.org/blog/2016/the-paediatric-regulation-a-work-in-progress/.
136. Smyth, R.L. and A.M. Weindling, *Research in children: ethical and scientific aspects.* Lancet, 1999. **354 Suppl 2**: p. SII21-4.
137. Simar, R., *Pediatric Drug Development: The International Conference on Harmonization Focus on Clinical Investigations in Children.* Drug Information Journal, 2000. **34**: p. 809-819.
138. Steinbrook, R., *Testing medications in children.* N Engl J Med, 2002. **347**(18): p. 1462-70.
139. Rheims, S., et al., *Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy.* PLoS Med, 2008. **5**(8): p. e166.
140. Smyth, R.L., *Research with children. Paediatric practice needs better evidence--gained in collaboration with parents and children.* BMJ, 2001. **322**(7299): p. 1377-8.
141. Roberts, R., et al., *Pediatric drug labeling: improving the safety and efficacy of pediatric therapies.* JAMA, 2003. **290**(7): p. 905-11.
142. Saint-Raymond, A., D. Brasseur, and N. Seigneuret, *[Medicines for children: time to act!].* Arch Pediatr, 2005. **12**(8): p. 1195-8.
143. Saint Raymond, A. and D. Brasseur, *Development of medicines for children in Europe: ethical implications.* Paediatr Respir Rev, 2005. **6**(1): p. 45-51.
144. Conroy, S., et al., *Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children.* BMJ, 2000. **320**(7227): p. 79-82.
145. Crawley, E.M., et al., *Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial.* Arch Dis Child, 2017.
146. ME Association. *The SMILE trial is published – with press release, science media centre 'expert reactions', and media coverage | 21 September 2017*. 2017 25 September 2017 May 2018].
147. Ginsberg, G.D., et al., *Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature.* Toxicological Sciences, 2002. **66**(2): p. 185–200.

148. Rocchi, F. and P. Tomasi, *The development of medicines for children. Part of a series on Pediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni.* Pharmacol Res, 2011. **64**(3): p. 169-75.
149. Sauer, P.J. and C.o.E.S.i.P. Ethics Working Group, *Research in children. A report of the Ethics Working Group of the CESP.* Eur J Pediatr, 2002. **161**(1): p. 1-5.
150. Crawley, E., *The epidemiology of chronic fatigue syndrome/myalgic encephalitis in children.* Arch Dis Child, 2014. **99**(2): p. 171-4.
151. Kessler, R.C., S. Avenevoli, and K. Ries Merikangas, *Mood disorders in children and adolescents: an epidemiologic perspective.* Biol Psychiatry, 2001. **49**(12): p. 1002-14.
152. Weller, E.B. and R.A. Weller, *Treatment options in the management of adolescent depression.* J Affect Disord, 2000. **61 Suppl 1**: p. 23-8.
153. Barsness, K.A., et al., *IL-1beta induces an exaggerated pro- and anti-inflammatory response in peritoneal macrophages of children compared with adults.* Pediatr Surg Int, 2004. **20**(4): p. 238-42.
154. Barsness, K.A., et al., *Endotoxin induces an exaggerated interleukin-10 response in peritoneal macrophages of children compared with adults.* J Pediatr Surg, 2004. **39**(6): p. 912-5; discussion 912-5.
155. Bylund, D.B. and A.L. Reed, *Childhood and Adolescent Depression: Why do Children and Adults Respond Differently to Antidepressant Drugs?* Neurochemistry international, 2007. **51**(5): p. 246-253.
156. Farrell, R., et al., *Barriers to participation in industry-sponsored clinical trials in pediatric type 2 diabetes.* Pediatr Diabetes, 2017. **18**(7): p. 574-578.
157. Rudolf, M.C., et al., *A search for the evidence supporting community paediatric practice.* Arch Dis Child, 1999. **80**(3): p. 257-61.
158. Caldwell, P.H., et al., *Clinical trials in children.* Lancet, 2004. **364**(9436): p. 803-11.
159. Bond, M.C. and S. Pritchard, *Understanding clinical trials in childhood cancer.* Paediatr Child Health, 2006. **11**(3): p. 148-50.
160. Ablett, S., C.R. Pinkerton, and G. United Kingdom Children's Cancer Study, *Recruiting children into cancer trials--role of the United Kingdom Children's Cancer Study Group (UKCCSG).* Br J Cancer, 2003. **88**(11): p. 1661-5.
161. Cancer Research UK. *Children's cancer statistics*. 2018; Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers Accessed: 10/05/2018.
162. Wishart, A., *One in three: a son's journey into the history of science and cancer* 2006: London: Profile Books.
163. Whelan, J.S. and L.A. Fern, *Poor accrual of teenagers and young adults into clinical trials in the UK.* Lancet Oncol, 2008. **9**(4): p. 306-7.
164. Tai, E., et al., *Understanding and addressing the lack of clinical trial enrollment among adolescents with cancer.* Pediatrics, 2014. **133 Suppl 3**: p. S98-s103.
165. Hough, R., et al., *Are survival and mortality rates associated with recruitment to clinical trials in teenage and young adult patients with acute lymphoblastic leukaemia? A retrospective observational analysis in England.* BMJ Open, 2017. **7**(10): p. e017052.
166. Children with Cancer UK. 2018 May 2018; Available from: https://www.childrenwithcancer.org.uk/get-involved/events/.

167. Cancer Research UK, *Race For Life.* 2018.
168. Nuffield Council on Bioethics, *Statement of aspiration: improving research by involving children and young people*. 2016.
169. Regulation No 1901/2006, *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/82/EC and Regulation (EC) No 726/2004.* . 2006, Official J Eur Comm L 378/1: European Parliament
170. European Medicines Agency. *Stimulating the development of medicines for children*. 2015 10/05/2018].
171. Gamble, C., et al., *New European Union regulation of clinical trials is conflicting on deferred consent in emergency situations.* BMJ, 2013. **346**: p. f667.
172. Luchtenberg, M., et al., *Young People's Experiences of Participation in Clinical Trials: Reasons for Taking Part.* Am J Bioeth, 2015. **15**(11): p. 3-13.
173. Healthtalk.org. *Young people's experience: Clinical trials & medical research*. 2018; Available from: http://www.healthtalk.org/young-peoples-experiences/clinical-trials-medical-research/topics.
174. Bower, P., et al., *Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities.* Trials, 2014. **15**: p. 399.
175. Treweek, S., et al., *Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis.* BMJ Open, 2013. **3**(2).
176. Healy, P., et al., *Identifying trial recruitment uncertainties using a James Lind Alliance Priority Setting Partnership - the PRioRiTy (Prioritising Recruitment in Randomised Trials) study.* Trials, 2018. **19**(1): p. 147.
177. Rooshenas, L., et al., *Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials.* PLoS Med, 2016. **13**(10): p. e1002147.
178. Jerosch-Herold, C., et al., *A questionnaire-based survey of participants' decisions regarding recruitment and retention in a randomised controlled trial - lessons learnt from the SCoRD trial.* Contemp Clin Trials, 2011. **32**(3): p. 363-8.
179. Ross, S., et al., *Barriers to participation in randomised controlled trials: a systematic review.* J Clin Epidemiol, 1999. **52**(12): p. 1143-56.
180. Howard, L., et al., *Why is recruitment to trials difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness.* Contemp Clin Trials, 2009. **30**(1): p. 40-6.
181. Toerien, M., et al., *A review of reporting of participant recruitment and retention in RCTs in six major journals.* Trials, 2009. **10**: p. 52.
182. Treweek, S., et al., *Meeting the challenges of recruitment to multicentre, community-based, lifestyle-change trials: a case study of the BeWEL trial.* Trials, 2013. **14**: p. 436.
183. McDonald, A.M., et al., *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies.* Trials, 2006. **7**: p. 9.
184. Schandelmaier, S., et al., *Premature Discontinuation of Randomized Trials in Critical and Emergency Care: A Retrospective Cohort Study.* Crit Care Med, 2016. **44**(1): p. 130-7.

185. Sully, B.G., S.A. Julious, and J. Nicholl, *A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies.* Trials, 2013. **14**: p. 166.
186. Gul, R.B. and P.A. Ali, *Clinical trials: the challenge of recruitment and retention of participants.* J Clin Nurs, 2010. **19**(1-2): p. 227-33.
187. Walters, S.J., et al., *Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme.* BMJ Open, 2017. **7**(3): p. e015276.
188. Kaur, G., *Recruitment to Randomised Controlled Trials with Children*, in *Psychology*. 2016, University of Liverpool.
189. Huntington, C., et al., *Lessons learned on recruitment and retention in hard-to-reach families in a phase III randomised controlled trial of preparatory information for children undergoing general anaesthesia.* BMC Oral Health, 2017. **17**(1): p. 122.
190. Dufetelle, E., G.W. t Jong, and F. Kaguelidou, *Randomized controlled trials in pediatric patients had higher completion rates than adult trials: a cross-sectional study.* J Clin Epidemiol, 2018. **100**: p. 53-60.
191. Amstutz, A., et al., *Discontinuation and non-publication of randomised clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study.* BMJ Open, 2017. **7**(7): p. e016216.
192. Alturki, R., et al., *Premature trial discontinuation often not accurately reflected in registries: comparison of registry records with publications.* J Clin Epidemiol, 2017. **81**: p. 56-63.
193. Ioannidis, J.P., *Clinical trials: what a waste.* Bmj, 2014. **349**: p. g7089.
194. Chapman, S.J., et al., *Discontinuation and non-publication of surgical randomised controlled trials: observational study.* BMJ, 2014. **349**: p. g6870.
195. Ross, J.S., et al., *Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis.* BMJ, 2012. **344**: p. d7292.
196. Ong, E.G., et al., *Randomized clinical trial of glutamine-supplemented versus standard parenteral nutrition in infants with surgical gastrointestinal disease.* Br J Surg, 2012. **99**(7): p. 929-38.
197. Smyth, R.M., et al., *The natural history of conducting and reporting clinical trials: interviews with trialists.* Trials, 2015. **16**: p. 16.
198. Stead, M., et al., *Understanding the potential and challenges of adenoma treatment as a prevention opportunity: insights from the BeWEL formative study.* Prev Med, 2012. **54**(1): p. 97-103.
199. Paramasivan, S., et al., *A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT - Quanti-Qualitative Appointment Timing.* Trials, 2015. **16**: p. 88.
200. Woolfall, K., et al., *Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting.* BMJ Open, 2014. **4**(5): p. e005045.
201. De Salis, I., et al., *Qualitative research to improve RCT recruitment: issues arising in establishing research collaborations.* Contemp Clin Trials, 2008. **29**(5): p. 663-70.
202. De Salis, I., et al., *Using qualitative research methods to improve recruitment to randomized controlled trials: the Quartet study.* J Health Serv Res Policy, 2008. **13 Suppl 3**: p. 92-6.

203. Avery, K.N., et al., *The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer--the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial.* Trials, 2014. **15**: p. 200.
204. Crawley, E., et al., *The feasibility and acceptability of conducting a trial of specialist medical care and the Lightning Process in children with chronic fatigue syndrome: feasibility randomized controlled trial (SMILE study).* Trials, 2013. **14**: p. 415.
205. Robinson, L., et al., *Identifying the participant characteristics that predict recruitment and retention of participants to randomised controlled trials involving children: a systematic review.* Trials, 2016. **17**(1): p. 294.
206. Fletcher, B., et al., *Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review.* BMJ Open, 2012. **2**(1): p. e000496.
207. Donovan, J.L., et al., *Development of a complex intervention improved randomization and informed consent in a randomized controlled trial.* J Clin Epidemiol, 2009. **62**(1): p. 29-36.
208. Lewin, S., C. Glenton, and A.D. Oxman, *Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study.* BMJ, 2009. **339**: p. b3496.
209. O'Cathain, A., et al., *Maximising the value of combining qualitative research and randomised controlled trials in health research: the QUAlitative Research in Trials (QUART) study--a mixed methods study.* Health Technol Assess, 2014. **18**(38): p. 1-197, v-vi.
210. Houghton, C., et al., *Factors that impact on recruitment to randomised trials in health care: a qualitative evidence synthesis (Protocol).* Cochrane Database of Systematic Reviews, 2017.
211. Rick, J., et al., *Systematic techniques for assisting recruitment to trials (START): study protocol for embedded, randomized controlled trials.* Trials, 2014. **15**(1): p. 407.
212. Treweek, S., et al., *Strategies to improve recruitment to randomised controlled trials.* Cochrane Database Syst Rev, 2010(1): p. MR000013.
213. Caldwell, P.H., et al., *Strategies for increasing recruitment to randomised controlled trials: systematic review.* PLoS Med, 2010. **7**(11): p. e1000368.
214. Parikh, Y., M. Mason, and K. Williams, *Researchers' perspectives on pediatric obesity research participant recruitment.* Clin Transl Med, 2016. **5**(1): p. 20.
215. Herbert, L.J., et al., *Factors Associated with Recruitment and Retention in Randomized Controlled Trials of Behavioral Interventions for Patients with Pediatric Type 1 Diabetes.* J Clin Psychol Med Settings, 2016. **23**(2): p. 112-25.
216. Hein, I.M., et al., *Why do children decide not to participate in clinical research: a quantitative and qualitative study.* Pediatr Res, 2015. **78**(1): p. 103-8.
217. Weintraub, J.A. and C.E. Breland, *Challenges, benefits, and factors to enhance recruitment and inclusion of children in pediatric dental research.* Int J Paediatr Dent, 2015. **25**(5): p. 310-6.
218. Hoberman, A., et al., *Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters.* JAMA Pediatr, 2013. **167**(6): p. 561-6.

219. Bhatnagar, S., et al., *Development and impact of an intervention to boost recruitment in a multicenter pediatric randomized clinical trial.* Clin Pediatr (Phila), 2014. **53**(2): p. 151-7.
220. Barratt, R., et al., *Why families choose not to participate in research: feedback from non-responders.* J Paediatr Child Health, 2013. **49**(1): p. 57-62.
221. Coutinho, M.T., et al., *Factors associated with recruitment and retention of diverse children with asthma.* Child Health Care, 2014. **43**(2): p. 132-150.
222. Tromp, K. and S. Vathorst, *Gatekeeping by Professionals in Recruitment of Pediatric Research Participants: Indeed an Undesirable Practice.* Am J Bioeth, 2015. **15**(11): p. 30-2.
223. Sharkey, K., et al., *Clinician gate-keeping in clinical research is not ethically defensible: an analysis.* J Med Ethics, 2010. **36**(6): p. 363-6.
224. Greenberg, R.G., et al., *Parents' perceived obstacles to pediatric clinical trial participation: Findings from the clinical trials transformation initiative.* Contemp Clin Trials Commun, 2018. **9**: p. 33-39.
225. O'Hara, C.B., et al., *A qualitative feasibility study to inform a randomised controlled trial of fluid bolus therapy in septic shock.* Arch Dis Child, 2018. **103**(1): p. 28-32.
226. Volkening, L.K., et al., *Recruitment Into a Pediatric Continuous Glucose Monitoring RCT.* J Diabetes Sci Technol, 2017. **11**(1): p. 100-107.
227. Farrington, C., et al., *Factors Affecting Recruitment of Participants for Studies of Diabetes Technology in Newly Diagnosed Youth with Type 1 Diabetes: A Qualitative Focus Group Study with Parents and Children.* Diabetes Technol Ther, 2016. **18**(9): p. 568-73.
228. Tait, A.R., et al., *Factors that influence parents' decisions to consent to their child's participation in clinical anesthesia research.* Anesth Analg, 1998. **86**(1): p. 50-3.
229. Patterson, C.A., et al., *Clinical Trial Decision Making in Pediatric Sickle Cell Disease: A Qualitative Study of Perceived Benefits and Barriers to Participation.* J Pediatr Hematol Oncol, 2015. **37**(6): p. 415-22.
230. Barakat, L.P., et al., *Initial development of a questionnaire evaluating perceived benefits and barriers to pediatric clinical trials participation.* Contemp Clin Trials, 2013. **34**(2): p. 218-26.
231. Sauers-Ford, H.S., et al., *Improving Recruitment and Retention Rates in a Randomized Controlled Trial.* Pediatrics, 2017. **139**(5).
232. Zwaanswijk, M., et al., *Young patients', parents', and survivors' communication preferences in paediatric oncology: results of online focus groups.* BMC Pediatr, 2007. **7**: p. 35.
233. Caldwell, P.H., *The Recruitment of Children to Randomised Controlled Trials*, in *Paediatrics and Child Health*. 2003, University of Sydney.
234. Breland-Noble, A.M., et al., *"Mama just won't accept this": adult perspectives on engaging depressed African American teens in clinical research and treatment.* J Clin Psychol Med Settings, 2011. **18**(3): p. 225-34.
235. May, D.E., et al., *Factors associated with recruitment and screening in the Treatment for Adolescents With Depression Study (TADS).* J Am Acad Child Adolesc Psychiatry, 2007. **46**(7): p. 801-10.
236. Breland-Noble, A.M., et al., *Engaging depressed African American adolescents in treatment: lessons from the AAKOMA PROJECT.* J Clin Psychol, 2010. **66**(8): p. 868-79.

237. Bean, M.K., et al., *Impact of motivational interviewing on engagement in a parent-exclusive paediatric obesity intervention: randomized controlled trial of NOURISH+MI.* Pediatr Obes, 2019. **14**(4): p. e12484.
238. Nguyen, T.T., et al., *Challenging recruitment of youth with type 2 diabetes into clinical trials.* J Adolesc Health, 2014. **54**(3): p. 247-54.
239. Close, S., et al., *Using information technology and social networking for recruitment of research participants: experience from an exploratory study of pediatric Klinefelter syndrome.* J Med Internet Res, 2013. **15**(3): p. e48.
240. Wendler, D. and T. Jenkins, *Children's and their parents' views on facing research risks for the benefit of others.* Arch Pediatr Adolesc Med, 2008. **162**(1): p. 9-14.
241. Franciscus, M., et al., *Recruitment and retention of participants for an international type 1 diabetes prevention trial: a coordinators' perspective.* Clin Trials, 2014. **11**(2): p. 150-8.
242. Banteka, M., V. Tailor, and A. Dahlmann-Noor, *Delivering clinical trials and observational studies in child eye health: a nationwide survey in the United Kingdom.* J Pediatr Ophthalmol Strabismus, 2015. **52**(2): p. 106-12.
243. Greenberg, R.G., et al., *Perceived barriers to pediatrician and family practitioner participation in pediatric clinical trials: Findings from the Clinical Trials Transformation Initiative.* Contemp Clin Trials Commun, 2018. **9**: p. 7-12.
244. Powell, K., et al., *Exceeding the recruitment target in a primary care paediatric trial: an evaluation of the Choice of Moisturiser for Eczema Treatment (COMET) feasibility randomised controlled trial.* Trials, 2016. **17**(1): p. 550.
245. Djulbegovic, B., *Uncertainty and equipoise: at interplay between epistemology, decision making and ethics.* Am J Med Sci, 2011. **342**(4): p. 282-9.
246. Donovan, J.L., et al., *The intellectual challenges and emotional consequences of equipoise contributed to the fragility of recruitment in six randomized controlled trials.* J Clin Epidemiol, 2014. **67**(8): p. 912-20.
247. Mills, N., et al., *Training recruiters to randomized trials to facilitate recruitment and informed consent by exploring patients' treatment preferences.* Trials, 2014. **15**: p. 323.
248. Wasiewski, W.W. and K.C. Johnston, *Clinical trials, devices, unproven treatments, and clinical equipoise.* Stroke, 2009. **40**(6): p. e441-2.
249. Warshaw, M.G., et al., *The interaction between equipoise and logistics in clinical trials: A case study.* Clinical Trials, 2017. **14**(3): p. 314-318.
250. Hetherton, J., A. Matheson, and M. Robson, *Recruitment by GPs during consultations in a primary care randomized controlled trial comparing computerized psychological therapy with clinical psychology and routine GP care: problems and possible solutions.* Primary Health Care Research and Development 2004. **5:** : p. 5–10.
251. Freedman, B., *Equipoise and the ethics of clinical research.* N Engl J Med, 1987. **317**(3): p. 141-5.
252. Hellman, S. and D.S. Hellman, *Of mice but not men. Problems of the randomized clinical trial.* N Engl J Med, 1991. **324**(22): p. 1585-9.
253. Lilford, R.J. and J. Jackson, *Equipoise and the ethics of randomization.* J R Soc Med, 1995. **88**(10): p. 552-9.

254. De Haan, E., et al., *Prediction of outcome and early vs. late improvement in OCD patients treated with cognitive behaviour therapy and pharmacotherapy.* Acta Psychiatr Scand, 1997. **96**(5): p. 354-61.
255. Gifford, F., *Freedman's 'clinical equipoise' and sliding-scale all-dimensions-considered equipoise'.* J Med Philos, 2000. **25**(4): p. 399-426.
256. van der Graaf, R. and J.J. van Delden, *Equipoise should be amended, not abandoned.* Clin Trials, 2011. **8**(4): p. 408-16.
257. Baum, M., *New approach for recruitment into randomised controlled trials: clinical trials are ethically impossible.* Lancet, 1993. **341**: p. 812-813.
258. Charles, C., A. Gafni, and T. Whelan, *Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango).* Soc Sci Med, 1997. **44**(5): p. 681-92.
259. Charles, C., A. Gafni, and T. Whelan, *Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model.* Soc Sci Med, 1999. **49**(5): p. 651-61.
260. Morris, A.D., A.L. Zaritsky, and G. LeFever, *Evaluation of ethical conflicts associated with randomized, controlled trials in critically ill children.* Crit Care Med, 2000. **28**(4): p. 1152-6.
261. Hales, G., A. Beveridge, and D. Smith, *The conflicting roles of clinicians versus investigators in HIV randomised clinical trials.* Culture, Health & Sexuality, 2001. **3**(1): p. 67-79.
262. Ulucanlar, S., *Randomised Controlled Trials and Equipoise*, in *Department of Social Medicine*. 2010, University of Bristol.
263. Ashcroft, R.E., et al., *Implications of socio-cultural contexts for the ethics of clinical trials.* Health Technol Assess, 1997. **1**(9): p. i-iv, 1-65.
264. Appelbaum, P.S., et al., *Therapeutic misconception in research subjects: development and validation of a measure.* Clin Trials, 2012. **9**(6): p. 748-61.
265. Dresser, R., *The ubiquity and utility of the therapeutic misconception.* Soc Philos Policy, 2002. **19**(2): p. 271-94.
266. Veatch, R.M., *Why researchers cannot establish equipoise.* Am J Bioeth, 2006. **6**(4): p. 55-7.
267. Veatch, R.M., *The irrelevance of equipoise.* J Med Philos, 2007. **32**(2): p. 167-83.
268. Jansen, L.A., *A closer look at the bad deal trial: beyond clinical equipoise.* Hastings Cent Rep, 2005. **35**(5): p. 29-36.
269. Sackett, D.L., *Equipoise, a term whose time (if it ever came) has surely gone.* CMAJ, 2000. **163**(7): p. 835-6.
270. Pletsch, P.K. and P.E. Stevens, *Inclusion of children in clinical research: Lessons learned from mothers of diabetic children.* Clinical Nursing Research, 2001. **10**: p. 140- 162.
271. Hey, S.P., et al., *Is the concept of clinical equipoise still relevant to research?* BMJ, 2017. **359**: p. j5787.
272. Hey, S.P., et al., *Research ethics for emerging trial designs: does equipoise need to adapt?* BMJ, 2018. **360**: p. k226.
273. Garcia, J., D. Elbourne, and C. Snowdon, *Equipoise: a case study of the views of clinicians involved in two neonatal trials.* Clin Trials, 2004. **1**(2): p. 170-8.
274. Ashcroft, R., *Equipoise, knowledge and ethics in clinical research and practice.* Bioethics, 1999. **13**(3-4): p. 314-26.

275. Marquis, D., *Leaving therapy to chance.* Hastings Cent Rep, 1983. **13**(4): p. 40-7.
276. Marquis, D., *An argument that all prerandomized clinical trials are unethical.* J Med Philos, 1986. **11**(4): p. 367-83.
277. Marquis, D., *How to resolve an ethical dilemma concerning randomized clinical trials.* N Engl J Med, 1999. **341**(9): p. 691-3.
278. Tomlin, Z., et al., *Patient advocacy and patient centredness in participant recruitment to randomized-controlled trials: implications for informed consent.* Health Expect, 2012.
279. King, M., et al., *Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.* Health technology assessment (Winchester, England), 2005. **9**(35): p. 1-186, iii-iv.
280. Harrop, E., et al., *Why do patients decline surgical trials? Findings from a qualitative interview study embedded in the Cancer Research UK BOLERO trial (Bladder cancer: Open versus Lapararoscopic or RObotic cystectomy).* Trials, 2016. **17**(1): p. 35.
281. Johnson, L.C., et al., *Sampling bias and other methodological threats to the validity of health survey research.* Int J Stress Mgmt, 2000. **7**((4)): p. 247–67.
282. Everitt, B.S., *Analysis of drop-out data in treatment trials.* Br J Psychiatry, 1998. **173**: p. 271.
283. Mills, E.J., et al., *Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors.* Lancet Oncol, 2006. **7**(2): p. 141-8.
284. McPherson, K. and A. Britton, *The impact of patient treatment preferences on the interpretation of randomised controlled trials.* Eur J Cancer, 1999. **35**(11): p. 1598-602.
285. Bell, M.L., et al., *Differential dropout and bias in randomised controlled trials: when it matters and when it may not.* BMJ, 2013. **346**: p. e8668.
286. Thorstensson, C.A., et al., *Choosing surgery: patients' preferences within a trial of treatments for anterior cruciate ligament injury. A qualitative study.* BMC Musculoskelet Disord, 2009. **10**: p. 100.
287. Steidtmann, D., et al., *Patient treatment preference as a predictor of response and attrition in treatment for chronic depression.* Depress Anxiety, 2012. **29**(10): p. 896-905.
288. Torgerson, D. and J.K. Moffett, *Patient preference and validity of randomized controlled trials.* JAMA, 2005. **294**(1): p. 41-2; author reply 42.
289. Preference Collaborative Review Group, et al., *Patients' preferences within randomised trials: systematic review and patient level meta-analysis*. Vol. 337. 2008.
290. Cook, T.D. and D.T. Campbell, *Quasi-experimentation: design and analysis issues for field settings*. 1979, Chicago: Rand McNally.
291. Morgan-Trimmer, S., et al., *Family preferences for home or hospital care at diagnosis for children with diabetes in the DECIDE study.* Diabet Med, 2016. **33**(1): p. 119-24.
292. King, M., et al., *Impact of participant and physician intervention preferences on randomized trials: a systematic review.* JAMA, 2005. **293**(9): p. 1089-99.
293. Kearney, A., et al., *Development of an online resource for recruitment research in clinical trials to organise and map current literature.* Clin Trials, 2018: p. 1740774518796156.

294. Bower, P., et al., *Patient preferences in randomised controlled trials: conceptual framework and implications for research.* Soc Sci Med, 2005. **61**(3): p. 685-95.
295. Bandura, A., *Self-efficacy: the exercise of control*. 1997, New York: : W.H. Freeman and Company.
296. Ashok, P.W., et al., *A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation.* Hum Reprod, 2002. **17**(1): p. 92-8.
297. Roland, M. and D. Torgerson, *Understanding controlled trials: what outcomes should be measured?* BMJ, 1998. **317**(7165): p. 1075.
298. Ghanizadeh, A., M.R. Mohammadi, and G.R. Dehbozorgi, *Children and Their Parent's Perceptions of Symptom Severity and Treatment Preference for Tourette Syndrome.* Iran J Psychiatry, 2010. **5**(3): p. 93-6.
299. Young, B., et al., *Parents' experiences of their children's presence in discussions with physicians about Leukemia.* Pediatrics, 2011. **127**(5): p. e1230-8.
300. Young, B., et al., *Managing communication with young people who have a potentially life threatening chronic illness: qualitative study of patients and parents.* BMJ, 2003. **326**(7384): p. 305.
301. Cahill, P. and A. Papageorgiou, *Triadic communication in the primary care paediatric consultation: a review of the literature.* Br J Gen Pract, 2007. **57**(544): p. 904-11.
302. Nguyen, B., et al., *Recruitment challenges and recommendations for adolescent obesity trials.* J Paediatr Child Health, 2012. **48**(1): p. 38-43.
303. Taylor, K.M., R.G. Margolese, and C.L. Soskolne, *Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer.* N Engl J Med, 1984. **310**(21): p. 1363-7.
304. Kaas, R., A.A. Hart, and E.J. Rutgers, *The impact of the physician on the accrual to randomized clinical trials in patients with primary operable breast cancer.* Breast, 2005. **14**(4): p. 310-6.
305. Phillips, L.J., et al., *Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics.* Aust N Z J Psychiatry, 2009. **43**(9): p. 818-29.
306. Young, B., Shilling, V., Hickey, H., Sowden, E., Smyth, R. L., & Williamson, P. R., *What parents think about being approached about children's trials, how this differs from what practitioners expect, and what this tells us about enhancing recruitment.* Trials,, 2011. **12(Suppl 1), A116.**
307. Varma, S., T. Jenkins, and D. Wendler, *How do children and parents make decisions about pediatric clinical research? .* Journal of Pediatric Hematology 2008. **30**(823-828).
308. Happ, M.B., et al., *Parent and child perceptions of a self-regulated, home-based exercise program for children with cystic fibrosis.* Nurs Res, 2013. **62**(5): p. 305-14.
309. Fogas, B.S., J.R. Oesterheld, and R.I. Shader, *A retrospective study of children's perceptions of participation as clinical research subjects in a minimal risk study.* J Dev Behav Pediatr, 2001. **22**(4): p. 211-6.
310. Wagner, K.D., M. Martinez, and T. Joiner, *Youths' and their parents' attitudes and experiences about participation in psychopharmacology treatment research.* J Child Adolesc Psychopharmacol, 2006. **16**(3): p. 298-307.

311. Broome ME, R.D., Hall JM. , *Children in Research: The Experience of Ill Children and Adolescents.* J Fam Nurs, 2001. **7:**: p. 32–49.
312. Cherrill, J., et al., *Clinical trials: the viewpoint of children.* Arch Dis Child, 2007. **92**(8): p. 712-3.
313. Cherrill, J., et al., *Clinical trials: the viewpoint of children with a chronic illness compared with healthy children.* Arch Dis Child, 2010. **95**(3): p. 229-32.
314. Wolthers, O.D., *A questionnaire on factors influencing children's assent and dissent to non-therapeutic research.* J Med Ethics, 2006. **32**(5): p. 292-7.
315. Stevens, P.E. and P.K. Pletsch, *Ethical issues of informed consent: mothers' experiences enrolling their children in bone marrow transplantation research.* Cancer Nurs, 2002. **25**(2): p. 81-7.
316. Masiye, F., et al., *Why mothers choose to enrol their children in malaria clinical studies and the involvement of relatives in decision making: evidence from Malawi.* Malawi Med J, 2008. **20**(2): p. 50-6.
317. Fisher, H.R., C. McKevitt, and A. Boaz, *Why do parents enroll their children in research: a narrative synthesis.* J Med Ethics, 2011. **37**(9): p. 544-51.
318. Vanhelst, J., et al., *Effect of child health status on parents' allowing children to participate in pediatric research.* BMC Med Ethics, 2013. **14**: p. 7.
319. Harth, S.C. and Y.H. Thong, *Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study.* BMJ, 1990. **300**(6736): p. 1372-5.
320. van Stuijvenberg, M., et al., *Informed consent, parental awareness, and reasons for participating in a randomised controlled study.* Arch Dis Child, 1998. **79**(2): p. 120-5.
321. Langley, J.M., et al., *Parental willingness to enter a child in a controlled vaccine trial.* Clin Invest Med, 1998. **21**(1): p. 12-6.
322. Tait, A.R., T. Voepel-Lewis, and S. Malviya, *Factors that influence parents' assessments of the risks and benefits of research involving their children.* Pediatrics, 2004. **113**(4): p. 727-32.
323. Glogowska, S.R., et al., *Who's Afraid of the Randomised Controlled Trial? Parents' Views of an SLT Research Study.* International Journal of Language & Communication Disorders, 2001. **Vol. 36, No. s1**: p. Pages 499-504.
324. McCann, S.K., M.K. Campbell, and V.A. Entwistle, *Reasons for participating in randomised controlled trials: conditional altruism and considerations for self.* Trials, 2010. **11**: p. 31.
325. Woodgate, R.L. and R.A. Yanofsky, *Parents' experiences in decision making with childhood cancer clinical trials.* Cancer Nurs, 2010. **33**(1): p. 11-8.
326. Jollye, *An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials.* Journal of Neonatal Nursing, 2009. **15**: p. 18-24.
327. Gammelgaard, A., L.E. Knudsen, and H. Bisgaard, *Perceptions of parents on the participation of their infants in clinical research.* Arch Dis Child, 2006. **91**(12): p. 977-80.
328. Hoehn, K.S., et al., *What factors are important to parents making decisions about neonatal research?* Arch Dis Child Fetal Neonatal Ed, 2005. **90**(3): p. F267-9.
329. Mason, S.A. and P.J. Allmark, *Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study.* Lancet, 2000. **356**(9247): p. 2045-51.

330. Hayman, R.M., et al., *Participation in research: informed consent, motivation and influence.* J Paediatr Child Health, 2001. **37**(1): p. 51-4.
331. Fairhead, J., M. Leach, and M. Small, *Public engagement with science? Local understandings of a vaccine trial in the Gambia.* J Biosoc Sci, 2006. **38**(1): p. 103-16.
332. Zupancic, J.A., et al., *Determinants of parental authorization for involvement of newborn infants in clinical trials.* Pediatrics, 1997. **99**(1): p. E6.
333. World Medical Organization, *Declaration of Helsinki*, in *Ethical Principles for Medical Research Involving Human Subjects*, W.M.A.D.o. Helsinki, Editor. 1964.
334. General Assembly of the World Medical, A., *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* J Am Coll Dent, 2014. **81**(3): p. 14-8.
335. Rothman, K.J., *Declaration of Helsinki should be strengthened.* BMJ, 2000. **321**(7258): p. 442-5.
336. Lilford, R.J. and B. Djulbegovic, *Declaration of Helsinki should be strengthened. Equipoise is essential principle of human experimentation.* BMJ, 2001. **322**(7281): p. 299-300.
337. Levine, R.J. and K.A. Lebacqz, *Ethical considerations in clinical trials.* Clin Pharmacol Ther, 1979. **25**(5): p. 728-41.
338. *Convention on the Rights of the Child.*, in *UN GA Res 44/25*. 1990.
339. Nuffield Council on Bioethics. *Children and clinical research: ethical issues: Stakeholder group meeting*. 2014; Available from: http://nuffieldbioethics.org/news/2014/young-people-assess-progress-of-council-s-project.
340. Woolfall, K., et al., *15 minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials.* Arch Dis Child Educ Pract Ed, 2015.
341. Roper, L., et al., *Children's views on research without prior consent in emergency situations: a UK qualitative study.* BMJ Open, 2018. **8**(6): p. e022894.
342. *ICH Guidelines for Good Clinical Practice E6(R1)*, T.I.C.f.H.o.T.R.f.P.f.H.U. (ICH), Editor. 1996.
343. Beauchamp T and C. J., *Principles of biomedical ethics*. 5th ed. 2001, Oxford:: Oxford University Press.
344. Leikin, S.L., *Minors' assent or dissent to medical treatment.* J Pediatr, 1983. **102**(2): p. 169-76.
345. National Institute for Health Research Clinical Research Network, *Introduction to good clinical practice (GCP): a practical guide to ethical and scientific quality standards in clinical research.* , N.C.W. Development, Editor. 2012: Leeds: .
346. Alderson, P., *Competent children? Minors' consent to health care treatment and research.* Soc Sci Med, 2007. **65**(11): p. 2272-83.
347. Broome, M.E., et al., *Children in research: new perspectives and practices for informed consent.* IRB, 2003. **Suppl 25**(5): p. S20-S23.
348. Kodish, E., *Informed consent for pediatric research: is it really possible?* J Pediatr, 2003. **142**(2): p. 89-90.
349. Chappuy, H., et al., *Parental consent in paediatric clinical research.* Arch Dis Child, 2006. **91**(2): p. 112-6.

350. Sammons, H.M., et al., *Research with children and young people: not on them.* Arch Dis Child, 2016. **101**(12): p. 1086-1089.
351. Tait, A.R., et al., *Improving the readability and processability of a pediatric informed consent document: effects on parents' understanding.* Arch Pediatr Adolesc Med, 2005. **159**(4): p. 347-52.
352. Caldwell, P.H., et al., *Standard 1: consent and recruitment.* Pediatrics, 2012. **129 Suppl 3**: p. S118-23.
353. Solomon-Moore, E., et al., *Roles of mothers and fathers in supporting child physical activity: a cross-sectional mixed-methods study.* BMJ Open, 2018. **8**(1): p. e019732.
354. Barkin, S.L., et al., *Changing overweight Latino preadolescent body mass index: the effect of the parent-child dyad.* Clin Pediatr (Phila), 2011. **50**(1): p. 29-36.
355. Clarke, J.L., et al., *Parent and child perceptions of school-based obesity prevention in England: a qualitative study.* BMC Public Health, 2015. **15**: p. 1224.
356. Hurling, R., et al., *Automated coaching to help parents increase their children's brushing frequency: an exploratory trial.* Community Dent Health, 2013. **30**(2): p. 88-93.
357. Crawley, E., et al., *Comparing specialist medical care with specialist medical care plus the Lightning Process for Chronic Fatigue Syndrome or Myalgic Encephalopathy (CFS/ME) Randomised Controlled Trial. SMILE – Specialist Medical Intervention & Lightning Evaluation*. 2012, University of Bristol.
358. Hutchings, N., et al., *CONTRACT Study - CONservative TReatment of Appendicitis in Children (feasibility): study protocol for a randomised controlled Trial.* Trials, 2018. **19**(1): p. 153.
359. Brigden, A., et al., *Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: study protocol.* BMJ Open, 2016. **6**(7): p. e011255.
360. Baos, S., et al., *Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to Activity Management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial.* Trials, 2018. **19**(1): p. 136.
361. Christie, D. and R. Viner, *Adolescent development.* BMJ, 2005. **330**(7486): p. 301-304.
362. Ondrusek, N., et al., *Empirical examination of the ability of children to consent to clinical research.* J Med Ethics, 1998. **24**(3): p. 158-65.
363. Crain, W.C., *Theories of Developmental Concepts and Applications.* . 1980, Englewood Cliffs, NJ, Prentice-Hall
364. Giedd, J.N., *Structural magnetic resonance imaging of the adolescent brain.* Ann N Y Acad Sci, 2004. **1021**: p. 77-85.
365. Tait, A.R., T. Voepel-Lewis, and S. Malviya, *Participation of children in clinical research: factors that influence a parent's decision to consent.* Anesthesiology, 2003. **99**(4): p. 819-25.
366. Modi, N., et al., *Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees.* Arch Dis Child, 2014. **99**(10): p. 887-91.

367. Royal College of Paediatrics Child Health: ethics advisory committee and D. Hull, *Guidelines for the ethical conduct of medical research involving children.* Arch.Dis.Child, 2000. **82**: p. 177-1.
368. Eder, M.L., et al., *Improving informed consent: suggestions from parents of children with leukemia.* Pediatrics, 2007. **119**(4): p. e849-59.
369. Yap, T.Y., et al., *A physician-directed intervention: teaching and measuring better informed consent.* Acad Med, 2009. **84**(8): p. 1036-42.
370. Johnson, L.M., et al., *Practical communication guidance to improve phase 1 informed consent conversations and decision-making in pediatric oncology.* Cancer, 2015. **121**(14): p. 2439-48.
371. Woolfall, K., et al., *How experience makes a difference: practitioners' views on the use of deferred consent in paediatric and neonatal emergency care trials.* BMC Med Ethics, 2013. **14**: p. 45.
372. Woolfall, K.e.a., *Research without prior consent (deferred consent) in trials investigating the emergency treatment of critically ill children: CONNECT study guidance*. 2015.
373. Young, B., et al., *Examining the validity of the unitary theory of clinical relationships: comparison of observed and experienced parent-doctor interaction.* Patient Educ Couns, 2011. **85**(1): p. 60-7.
374. Gamble, C., et al., *What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey.* PLoS One, 2012. **7**(5): p. e35982.
375. Scherer, D.G., *The capacities of minors to exercise voluntariness in medical treatment decisions.* Law Hum Behav, 1991. **15**(4): p. 431-49.
376. Abramovitch, R., et al., *Children's capacity to agree to psychological research: knowledge of risks and benefits and voluntariness.* Ethics Behav, 1995. **5**(1): p. 25-48.
377. Appelbaum, P.S., C.W. Lidz, and R. Klitzman, *Voluntariness of consent to research: a conceptual model.* Hastings Cent Rep, 2009. **39**(1): p. 30-9.
378. Mamotte, N. and D. Wassenaar, *Measuring voluntariness of consent to research: an instrument review.* J Empir Res Hum Res Ethics, 2015. **10**(2): p. 121-31.
379. Gillies, K. and V.A. Entwistle, *Supporting positive experiences and sustained participation in clinical trials: looking beyond information provision.* J Med Ethics, 2012. **38**(12): p. 751-6.
380. Young, B., et al., *Is communication guidance mistaken? Qualitative study of parent-oncologist communication in childhood cancer.* Br J Cancer, 2013. **109**(4): p. 836-43.
381. Sureshkumar, P., et al., *Parental consent to participation in a randomised trial in children: associated child, family, and physician factors.* Clin Trials, 2012. **9**(5): p. 645-51.
382. Forsey, M., et al., *Comparing doctors' and nurses' accounts of how they provide emotional care for parents of children with acute lymphoblastic leukaemia.* Psychooncology, 2013. **22**(2): p. 260-7.
383. Unguru, Y., A.M. Sill, and N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent.* Pediatrics, 2010. **125**(4): p. e876-83.
384. General Medical Council. *Good Practice in Research and Consent to Research*. 2013 May 2018]; Available from: https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors.

385. Joseph, P.D., J.C. Craig, and P.H.Y. Caldwell, *Clinical trials in children.* British Journal of Clinical Pharmacology, 2013 (December 10).
386. Brody, J.L., et al., *Enrolling adolescents in asthma research: adolescent, parent, and physician influence in the decision-making process.* J Asthma, 2009. **46**(5): p. 492-7.
387. Tates, K., et al., *Joking or Decision-Making? Affective and Instrumental Behaviour in Doctor-Parent-Child Communication.* Psychol Health, 2002. **17**: p. 281-295.
388. Tates, K., et al., *I've come for his throat': roles and identities in doctor-parent-child communication.* Child Care Health Dev, 2002. **28**(1): p. 109-16.
389. Tates, K., et al., *Doctor-parent-child relationships: a 'pas de trois'.* Patient Educ Couns, 2002. **48**(1): p. 5-14.
390. Wassmer, E., et al., *How do paediatricians communicate with children and parents?* Acta Paediatr, 2004. **93**(11): p. 1501-6.
391. Nova, C., E. Vegni, and E.A. Moja, *The physician-patient-parent communication: a qualitative perspective on the child's contribution.* Patient Educ Couns, 2005. **58**(3): p. 327-33.
392. Van Dulmen A, M., *Children's contribution to pediatric outpatient consultation.* Pediatrics, 1998. **3:563–8.**
393. Tates, K. and L. Meeuwesen, *'Let mum have her say': turntaking in doctor-parent-child communication.* Patient Educ Couns, 2000. **40**(2): p. 151-62.
394. Coyne, I., *Children's participation in consultations and decision-making at health service level: a review of the literature.* International journal of nursing studies, 2008. **45**(11): p. 1682-9.
395. Coyne, I. and P. Gallagher, *Participation in communication and decision-making: children and young people's experiences in a hospital setting.* J Clin Nurs, 2011. **20**(15-16): p. 2334-43.
396. Coyne, I., et al., *Children's participation in shared decision-making: children, adolescents, parents and healthcare professionals' perspectives and experiences.* Eur J Oncol Nurs, 2014. **18**(3): p. 273-80.
397. Tates, K. and L. Meeuwesen, *Doctor-parent-child communication. A (re)view of the literature.* Soc Sci Med, 2001. **52**(6): p. 839-51.
398. Blake, D., et al., *Adolescent perspectives on informed assent for an HIV vaccine trial. .* Journal of Adolescent Health, 2010. **46**: p. S28.
399. Coyne, I. and M. Harder, *Children's participation in decision-making: balancing protection with shared decision-making using a situational perspective.* J Child Health Care, 2011. **15**(4): p. 312-9.
400. Coyne, I., et al., *Interventions for promoting participation in shared decision-making for children with cancer.* Cochrane Database Syst Rev, 2013. **6**: p. Cd008970.
401. O'Cathain, A., *A Practical Guide to Using Qualitative Research with Randomized Controlled Trials*. 2018, United Kingdom: Oxford University Press.
402. O'Reilly, P., L. Martin, and G. Collins, *Few patients with prostate cancer are willing to be randomised to treatment.* BMJ : British Medical Journal, 1999. **318**(7197): p. 1556-1556.
403. Livesey, J., et al., *Trial of randomisation between radical prostatectomy and radiotherapy in early prostate cancer.* Clinical Oncology, 2000. **12**(63).

404. Donovan, J.L., et al., *Development of a complex intervention improved randomization and informed consent in a randomized controlled trial.* J.Clin Epidemiol., 2009. **62**(1): p. 29-36.
405. Mills, N., et al., *Exploring treatment preferences facilitated recruitment to randomized controlled trials.* J Clin Epidemiol, 2011. **64**(10): p. 1127-36.
406. Wade, J., et al., *It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials.* Social science & medicine (1982), 2009. **68**(11): p. 2018-28.
407. Mills, N., et al., *Addressing patient treatment preferences at trial recruitment*, in *Clinical Trials Methodology Conference 2011*. 2011, Trials 2011.
408. Donovan, J.L., et al., *Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI).* Trials, 2016. **17**(1): p. 283.
409. Wade, J., et al., *It's not just what you say, it's also how you say it: Opening the 'black box' of informed consent appointments in randomised controlled trials.* Soc.Sci.Med., 2009. **68**(11): p. 2018-2028.
410. Treweek, S., et al., *Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)?* Trials, 2018. **19**(1): p. 139.
411. Clarke, M., et al., *The SWAT (study within a trial) programme; embedding trials to improve the methodological design and conduct of future research.* Trials, 2015. **16**(Suppl 2): p. P209-P209.
412. Smith, V., et al., *SWAT-1: The effectiveness of a 'site visit' intervention on recruitment rates in a multi-centre randomised trial.* Trials, 2015. **16**: p. 211.
413. Cockayne, S., et al., *An optimised patient information sheet did not significantly increase recruitment or retention in a falls prevention study: an embedded randomised recruitment trial.* Trials, 2017. **18**(1): p. 144.
414. Constantin, A. *SWAT 36: Training in obtaining informed consent for clinical trials*. (2016 MAR 13 1417) 2016.
415. Jackson, C.J., et al., *Women's views and experiences of a patient preference trial in surgery: a qualitative study of the CARPET1 trial.* Clinical trials (London, England), 2010. **7**(6): p. 696-704.
416. Madsen, S.M., S. Holm, and P. Riis, *Attitudes towards clinical research among cancer trial participants and non-participants: an interview study using a Grounded Theory approach.* Journal of Medical Ethics, 2007. **33**(4): p. 234.
417. Wilson, C., et al., *Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework.* Trials, 2018. **19**(1): p. 50.
418. Hoddinott, P., J. Britten, and R. Pill, *Why do interventions work in some places and not others: a breastfeeding support group trial.* Soc Sci Med, 2010. **70**(5): p. 769-78.
419. Farquhar, M., et al., *The experience of using the SEIQoL-DW with patients with advanced chronic obstructive pulmonary disease (COPD): issues of process and outcome.* Quality of Life Research, 2010. **19**(5): p. 619-629.
420. Ritchie, J. and J. Lewis, *Qualitative research practice. A guide for social science students and researchers*. 2nd Edition ed, ed. J.L. Edited by Jane Ritchie, Carol McNaughton Nicholls, & Rachel Ormston. 2003, London: Sage.
421. Britten, N., *Qualitative interviews in medical research.* BMJ, 1995. **311**(6999): p. 251-3.
422. Braun, V. and V. Clarke, *Successful Qualitative Research: A Practical Guide for Beginners*. 2013, London: Sage Publications Ltd.

423. May, T., *Social Research: Issues, Methods and Process*. 2001: Maidenhead: Open University Press. Third Edition.
424. Holstein, J.A. and J.F. Gubrium, *The Active Interview*. Research Methods. 1995, London: Sage.
425. Morse, J.M., *Situating grounded theory within qualitative inquiry*. Using grounded theory in nursing, ed. R.S.S. Edited by Schreiber, P.N. 2001, New York: Springer Publishing Company.
426. Murray, S.A., et al., *Use of serial qualitative interviews to understand patients' evolving experiences and needs.* BMJ, 2009. **339**.
427. Salmon, P., N. Mendick, and B. Young, *Integrative qualitative communication analysis of consultation and patient and practitioner perspectives: towards a theory of authentic caring in clinical relationships.* Patient Educ Couns, 2011. **82**(3): p. 448-54.
428. O'Reilly, M. and N. Dogra, *Interviewing Children and Young People for Research*, ed. J. Seaman. 2017, London: Sage Publications Ltd.
429. Kvale, S., *Doing Interviews*. The Sage Qualitative Research Kit, ed. U. Flick. 2007, London: Sage Publications Ltd.
430. Christensen, P.H., *Children's participation in ethnographic research: Issues of power and representation.* 2004. **18**(2): p. 165-176.
431. Goodenough, T., et al., *Ethical protection in research: including children in the debate.* . Researchers and their 'subjects', ed. W.E.e. In Smyth M. 2004, Bristol: Policy Press.
432. Gallagher, M., *'Power is not an evil': rethinking power in participatory methods.* Children's Geographies, 2008. **6**(2): p. 137-150.
433. Williams, B., *Meaningful Consent to Participate in Social Research on the Part of People under the Age of Eighteen.* Research Ethics Review 2006. **Vol 2**(No 1): p. 19–24.
434. Masson, J., *Researching children's perspectives: legal issues.* . Researching Children's Perspectives ed. A. Lewis and G. Lindsay. 2000, Buckingham: Open University Press.
435. Horsley, K. and A. McCabe. *The Evaluator's Cookbook: Exercises for Participatory Evaluation with Children* 2008; Available from: http://www.bath.ac.uk/marketing/public-engagement/assets/the_evaluators_cookbook_participatory_evaluation_exercises_for_young_people.pdf.
436. Thomas, N. and C. O'Kane, *The ethics of participatory research with children.* Children & Society, 2006. **12**(5): p. 336-348.
437. Irwin, L.G. and J. Johnson, *Interviewing Young Children: Explicating Our Practices and Dilemmas.* 2005. **15**(6): p. 821-831.
438. Minichiello, V., R. Aroni, and T. Hays, *In-depth interviewing: Principles, techniques, analysis* ed. T. Edition. 2008, Melbourne, VIC: Longman Cheshire.
439. Silverman, D., *Doing Qualitative Research: A Practical Handbook*. Fourth Edition ed. 2013: Sage.
440. Kanagasabai, P.S., et al., *A Child-centered Method of Interviewing Children with Movement Impairments.* Phys Occup Ther Pediatr, 2018. **38**(3): p. 255-268.
441. Kara, H., *Research and Evaluation for Busy Students and Practitioners: A Time Saving Guide*. 2nd Edition ed. 2017, Bristol: Policy Press.

442. Gardner, H. and D. Randall, *The effects of the presence or absence of parents on interviews with children.* Nurse Res, 2012. **19**(2): p. 6-10.
443. Redsell, S. and A.M. Hastings, *Listening to Children and Young People in Healthcare Consultations*. 2010: Radcliffe Publishing.
444. Deakin, H. and K. Wakefield, *Skype interviewing: reflections of two PhD researchers.* Qualitative Research, 2014. **14**(5): p. 603-616.
445. Novick, G., *Is there a bias against telephone interviews in qualitative research?* Res Nurs Health, 2008. **31**(4): p. 391-8.
446. Holt, A., *Using the telephone for narrative interviewing: a research note.* Qualitative Research, 2010. **10**(1): p. 113–121.
447. Sturges, J.E. and K.J. Hanrahan, *Comparing Telephone and Face-to-Face Qualitative Interviewing: a Research Note.* 2004. **4**(1): p. 107-118.
448. Whale, K., et al., *'What does that mean?': a qualitative exploration of the primary and secondary clinical care experiences of young people with continence problems in the UK.* BMJ Open, 2017. **7**(10): p. e015544.
449. Haig-Ferguson, A., et al., *The use of Skype for delivering therapy in a Specialist Paediatric Chronic Fatigue Service; the dichotomy between restricting and enabling communication: a qualitative study.* British Journal of Health Psychology [submitted for publication 2018].
450. Oltmann, S.M., *Qualitative Interviews: A Methodological Discussion of the Interviewer and Respondent Contexts.* Information Science Faculty Publications
2016. **32**.
451. Hoser, B. and T. Nitschke, *Questions on ethics for research in the virtually connected world.* Social Networks, 2010. **32**(3): p. 180–186.
452. Hay-Gibson, N.V., *Interviews via VoIP: benefits and disadvantages within a PhD study of SMEs.* Library and Information Research, 2009. **33**(105): p. 39–50.
453. O'Connor, H., et al., *Internet-based interviewing*. The SAGE Handbook of Online Research Methods. , ed. N. Fielding, N. Lee, and G. Blank. Vol. 271–289. 2008, London: Sage.
454. Garton, S. and F. Copland, *'I like this interview; I get cakes and cats!': the effect of prior relationships on interview talk.* Qualitative Research, 2010. **10**(5): p. 533-551.
455. McEvoy, P., *Interviewing colleagues: addressing the issues of perspective, inquiry and representation.* Nurse Res, 2001. **9**(2): p. 49-59.
456. McQueen, A., et al., *Behind closed doors: physician-patient discussions about colorectal cancer screening.* J Gen Intern Med, 2009. **24**(11): p. 1228-35.
457. Lawton, J., et al., *Uncovering the emotional aspects of working on a clinical trial: a qualitative study of the experiences and views of staff involved in a type 1 diabetes trial.* Trials, 2015. **16**: p. 3.
458. Hammersley, M. and P. Atkinson, *Ethnography : principles in practice*. 1989, London ; New York.: Routledge.
459. McLeod, J., *Qualitative Research in Counselling and Psychotherapy*. 2001, London: Sage.
460. Winter, G., *A comparative discussion of the notion of validity in qualitative and quantitative research.* The Qualitative Report, 2000. **4**(3).
461. Denzin, N.K., *sociological methods: A sourcebook* (2nd ed.) ed. 1978, New York: McGraw Hill.

462. Barbour, R.S., *Checklists for improving rigour in qualitative research: a case of the tail wagging the dog?* BMJ, 2001. **322**(7294): p. 1115-7.
463. Tracy, S.J., *Qualitative Quality: Eight "Big-Tent" Criteria for Excellent Qualitative Research.* Qualitative Inquiry, 2010. **16**(10): p. 837-851.
464. Lincoln, Y.S. and E.G. Guba, *Naturalistic inquiry*. 1985, Newbury Park, CA: Sage.
465. NICE: National Institute for Health and Clinical Excellence, *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) Diagnosis and management of CFS/ME in adults and children.*, N.I.f.H.a.C. Excellence., Editor. 2007, Developed by the National Collaborating Centre for Primary Care: London.
466. Carter, B.D., et al., *Psychological symptoms in chronic fatigue and juvenile rheumatoid arthritis.* Pediatrics, 1999. **103**(5): p. 975-979.
467. Van Middendorp, H., et al., *Psychological adjustment of adolescent girls with chronic fatigue syndrome.* Pediatrics, 2001. **107**(3): p. E35.
468. Crawley, E., L. Hunt, and P. Stallard, *Anxiety in children with CFS/ME.* Eur.Child Adolesc.Psychiatry, 2009.
469. Bould, H., et al., *Depression and anxiety in children with CFS/ME: cause or effect?* Arch.Dis.Child, 2010.
470. Bell, D.S., K. Jordan, and M. Robinson, *Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome.* Pediatrics, 2001. **107**(5): p. 994-998.
471. Crawley, E.M., A.M. Emond, and J.A. Sterne, *Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics.* BMJ Open, 2011. **1**(2): p. e000252.
472. Rangel, L., et al., *The course of severe chronic fatigue syndrome in childhood.* J.R.Soc.Med., 2000. **93**(3): p. 129-134.
473. Joyce, J., M. Hotopf, and S. Wessely, *The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review.* QJM., 1997. **90**(3): p. 223-233.
474. Rimes, K.A., et al., *Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study.* Pediatrics, 2007. **119**(3): p. e603-e609.
475. Collin, S.M., et al., *Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts.* BMJ Open, 2015. **5**(10): p. e008830.
476. Royal College of Paediatrics and Child Health, *Evidence Based Guideline for the Management of CFS/ME (Chronic Fatigue Syndrome/Myalgic Encephalopathy) in Children and Young People*. 2004: London.
477. Loades, M., A. Brigden, and E. Crawley, *Current treatment approaches for paediatric CFS/ME.* Paediatr Child Health (Oxford), 2017. **27**(9): p. 432-434.
478. St Peter, S.D., et al., *Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial.* J Pediatr Surg, 2008. **43**(6): p. 981-5.
479. Rollins, K.E. and D.N. Lobo, *Non-operative management of uncomplicated acute appendicitis in children: where is the evidence?* Arch Dis Child, 2017. **102**(12): p. 1099-1100.
480. NICE: National Institute for Health and Clinical Excellence. *Appendicitis* 2016 [Accessed May 2018]].

481. Canty, T.G., Sr., et al., *Laparoscopic appendectomy for simple and perforated appendicitis in children: the procedure of choice?* J Pediatr Surg, 2000. **35**(11): p. 1582-5.
482. Varadhan, K.K., K.R. Neal, and D.N. Lobo, *Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials.* BMJ, 2012. **344**: p. e2156.
483. Lee, S.L., et al., *Does age affect the outcomes and management of pediatric appendicitis?* J Pediatr Surg, 2011. **46**(12): p. 2342-5.
484. Mizrahi, I., et al., *Comparison of pediatric appendectomy outcomes between pediatric surgeons and general surgery residents.* J Surg Res, 2013. **180**(2): p. 185-90.
485. Tiboni, S., et al., *Outcome of appendicectomy in children performed in paediatric surgery units compared with general surgery units.* Br J Surg, 2014. **101**(6): p. 707-14.
486. Hall, N.J., et al., *Is interval appendicectomy justified after successful nonoperative treatment of an appendix mass in children? A systematic review.* J Pediatr Surg, 2011. **46**(4): p. 767-71.
487. Armstrong, J., et al., *Non-operative management of early, acute appendicitis in children: is it safe and effective?* J Pediatr Surg, 2014. **49**(5): p. 782-5.
488. Svensson, J.F., et al., *Recurrence of acute appendicitis after non-operative treatment of appendiceal abscess in children: a single-centre experience.* Pediatr Surg Int, 2014. **30**(4): p. 413-6.
489. Georgiou, R., et al., *Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis.* Pediatrics, 2017. **139**(3).
490. Bowers, W.F., C.W. Hughes, and K.B. Bonilla, *The treatment of acute appendicitis under suboptimal conditions.* U S Armed Forces Med J, 1958. **9**(11): p. 1545-57.
491. Vons, C., et al., *Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial.* Lancet, 2011. **377**(9777): p. 1573-9.
492. Styrud, J., et al., *Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial.* World J Surg, 2006. **30**(6): p. 1033-7.
493. Hansson, J., et al., *Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients.* Br J Surg, 2009. **96**(5): p. 473-81.
494. Eriksson, S. and L. Granstrom, *Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis.* Br J Surg, 1995. **82**(2): p. 166-9.
495. Mason, R.J., *Non-operative management of uncomplicated acute appendicitis: using antibiotics is effective and decreases morbidity.* Evid Based Med, 2013. **18**(2): p. 67-8.
496. Liu, K. and L. Fogg, *Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis.* Surgery, 2011. **150**(4): p. 673-83.
497. Turhan, A.N., et al., *Comparison of operative and non operative management of acute appendicitis.* Ulus Travma Acil Cerrahi Derg, 2009. **15**(5): p. 459-62.
498. Hall, N.J., et al., *Active observation versus interval appendicectomy after successful non-operative treatment of an appendix mass in children (CHINA*

study): an open-label, randomised controlled trial. Lancet Gastroenterol Hepatol, 2017. **2**(4): p. 253-260.
499. Nitecki, S., A. Assalia, and M. Schein, *Contemporary management of the appendiceal mass.* Br J Surg, 1993. **80**(1): p. 18-20.
500. Eriksson, S. and J. Styrud, *Interval appendicectomy: a retrospective study.* Eur J Surg, 1998. **164**(10): p. 771-4; discussion 775.
501. Puri, P., et al., *Appendix mass in the very young child.* J Pediatr Surg, 1981. **16**(1): p. 55-7.
502. Freitas, M.S. and P.L. Glick, *Interval appendectomy for acute appendicitis.* J Pediatr Surg, 2009. **44**(5): p. 1056-8.
503. Svensson, J.F., et al., *Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial.* Ann Surg, 2015. **261**(1): p. 67-71.
504. Minneci, P.C., et al., *Feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children.* J Am Coll Surg, 2014. **219**(2): p. 272-9.
505. Gorter, R.R., et al., *Initial antibiotic treatment for acute simple appendicitis in children is safe: Short-term results from a multicenter, prospective cohort study.* Surgery, 2015. **157**(5): p. 916-23.
506. National Surgical Research Collaborative, *Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy.* British Journal of Surgery, 2013. **100**(9).
507. Beasant, L., N. Mills, and E. Crawley, *Adolescents and mothers value referral to a specialist service for chronic fatigue syndrome or myalgic encephalopathy (CFS/ME).* Prim Health Care Res Dev, 2013: p. 1-9.
508. ME Association. *Complementary treatments*. 2018; Available from: http://www.meassociation.org.uk/about/complementary-treatments/.
509. White, P., et al., *Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial.* Lancet., 2011. **377**(9768): p. 823-836.
510. Nijhof, S.L., et al., *Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial.* Lancet, 2012. **379**(9824): p. 1412-8.
511. Barbour, R.S., *The role of qualitative research in broadening the 'evidence base' for clinical practice.* J Eval Clin Pract, 2000. **6**(2): p. 155-63.
512. Popper K, *The Logic of Scientific Discovery.* . 1959 London: Hutchinson.
513. Clark, A.M., *The qualitative-quantitative debate: moving from positivism and confrontation to post-positivism and reconciliation.* J Adv Nurs, 1998. **27**(6): p. 1242-9.
514. Guba, E.G. and Y.S. Lincoln, *The Sage Handbook of Qualitative Research*. 3rd Edition ed. Chapter 8; Paradigmatic Controversies, contradictions and emerging confluences. 2005, london: Sage.
515. Henwood, K. and N. Pidgeon, *Beyond the qualitative paradigm: A framework for introducing diversity within qualitative psychology.* Journal of Community and Applied Social Psychology, 1994. **4**(4): p. 225-238.
516. Burr, V., *Social Constructionism*. 2003, London: Routledge.
517. Potter, J. and Wetherell, *Discourse and social psychology: Beyond attitudes and behaviour*. 1987, London: Sage.

518. Madill, A., A. Jordan, and C. Shirley, *Objectivity and reliability in qualitative analysis: realist, contextualist and radical constructionist epistemologies.* Br J Psychol, 2000. **91 (Pt 1)**: p. 1-20.
519. Tebes, J.K., *Community science, philosophy of science, and the practice of research.* Am J Community Psychol, 2005. **35**(3-4): p. 213-30.
520. Beasant, L., et al., *A systematic review and qualitative synthesis of literature reporting treatment preference in paediatric randomised controlled trials.* . 2015.
521. Petticrew, M. and H. Roberts, *Systematic Reviews in the Social Sciences A PRACTICAL GUIDE*. 2006, 350 Main Street, Malden, MA 02148-5020, USA: Blackwell Publishing.
522. Chappuy, H.F., A. C.; De Haut De Sigy, A., *Parental comprehension and decision in informed consent in pediatric clinical trials. [French].* Revue d'Oncologie Hematologie Pediatrique, 2014. **2**(2014376989): p. 65-69.
523. Hissink Muller, P.C.E., et al., *Parental preferences for treatment: Preliminary report from a randomised comparison of treatment strategies in (early) juvenile idiopathic arthritis (BeSt for Kids trial).* Pediatric Rheumatology, 2011. **9**: p. 8.
524. Hissink Muller, P.C.E., et al., *Randomized clinical trial in pediatric rheumatology: Are parents and patients in equipoise?* Arthritis and Rheumatism, 2012. **64**: p. S849.
525. Johnson, S.B., et al., *Participant and parent experiences in the parenteral insulin arm of the diabetes prevention trial for type 1 diabetes.* Diabetes Care, 2007. **30**(9): p. 2193-8.
526. Johnson, S.B., et al., *Participant and parent experiences in the oral insulin study of the Diabetes Prevention Trial for Type 1 Diabetes.* Pediatr Diabetes, 2009. **10**(3): p. 177-83.
527. Covidence, *A product by Alfred Health*. 2013.
528. Gough, D., J. Thomas, and S. Oliver, *Clarifying differences between review designs and methods.* Syst Rev, 2012. **1**: p. 28.
529. Sandelowski, M., et al., *Mapping the Mixed Methods-Mixed Research Synthesis Terrain.* J Mix Methods Res, 2012. **6**(4): p. 317-331.
530. QSR International Pty Ltd, *NVivo qualitative data analysis Software; Version 10*. 2012.
531. Allmark, P. and S. Mason, *Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process.* J Med Ethics, 2006. **32**(8): p. 439-43.
532. Critical Appraisal Skills Program (CASP). *Qualitative Research Checklist*. 2013 [cited 2013 31.05.13]; Available from: http://www.casp-uk.net/#!casp-tools-checklists/c18f8.
533. Dixon-Woods, M., et al., *Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods.* J Health Serv Res Policy, 2007. **12**(1): p. 42-7.
534. Malpass, A., et al., *"Medication career" or "moral career"? The two sides of managing antidepressants: a meta-ethnography of patients' experience of antidepressants.* Soc Sci Med, 2009. **68**(1): p. 154-68.
535. Noblit, G.H. and R.D. Hare, *Meta-Ethnography: Synthesising Qualitative Studies*. 1988, California Newbury Park.
536. Schutz, A., *Collected Papers* The Hague , Martinus Nijhoff; , 1971. **Volume 1.** .

537. Britten, N., et al., *Using meta ethnography to synthesise qualitative research: a worked example.* J Health Serv Res Policy, 2002. **7**(4): p. 209-15.
538. Atkins, S., et al., *Conducting a meta-ethnography of qualitative literature: lessons learnt.* BMC Med Res Methodol, 2008. **8**: p. 21.
539. Campbell, R., et al., *Evaluating meta-ethnography: systematic analysis and synthesis of qualitative research.* Health Technol Assess, 2011. **15**(43): p. 1-164.
540. Donovan, J.L., et al., *Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials.* Trials, 2014. **15**: p. 5.
541. Patton, M.Q., *Qualitative Research & Evaluation Methods: Integrating Theory and Practice*. 4th Edition ed. 2015, London: Sage Publications Ltd.
542. Charmaz, K., *Grounded Theory: Objectivist and Constructivist Methods*. 2nd Edition ed. Handbook of Qualitative Research, ed. N.K. Denzin and Y.S. Lincoln. 2000, London: Sage Publications Inc.
543. Glaser, B. and A. Strauss, *The discovery of grounded theory: Strategies for qualitative research.* 1999, New York: Aldine de Gruyter.
544. Gale, N.K., et al., *Using the framework method for the analysis of qualitative data in multi-disciplinary health research.* BMC Med Res Methodol, 2013. **13**: p. 117.
545. Glaser & Strauss, *The Discovery of Grounded Theory*. 1967, USA: Aldine Transaction: New Brunswick, NJ; .
546. Strauss and Corbin, *Basics of Qualitative Research*. 1998: Thousand Oaks CA: Sage Publications.
547. Charmaz, K., *Constructing Grounded Theory: A Practical Guide.* . 2006: SAGE Publications Ltd.
548. Braun, V. and V. Clarke, *Using Thematic Analysis in Psychology.* Qual.Res.Psych., 2006. **3**: p. 77-101.
549. Pigeon, N. and K. Henwood, *Grounded Theory: The hadbook ofdata analysis*. Vol. In M. Hardy A. Bryman (Eds). 2004, London: Sage.
550. Mays, N. and C. Pope, *Qualitative research in health care. Assessing quality in qualitative research.* BMJ, 2000. **320**(7226): p. 50-2.
551. Sandelowski, M., *Real qualitative researchers do not count: the use of numbers in qualitative research.* Res Nurs Health, 2001. **24**(3): p. 230-40.
552. Elo, S. and H. Kyngas, *The qualitative content analysis process.* J Adv Nurs, 2008. **62**(1): p. 107-15.
553. Hsieh, H.F. and S.E. Shannon, *Three approaches to qualitative content analysis.* Qual Health Res, 2005. **15**(9): p. 1277-88.
554. Prasad, B.D., *Content Analysis. A method in Social Science Research*, in *Research Methods for Social Work.*, I.D.K.L.D. (ed). Editor. 2008, Rawat Publication.: New Delhi:. p. (pp.174-193).
555. Cole, F.L., *Content analysis: process and application.* Clin Nurse Spec, 1988. **2**(1): p. 53-7.
556. Krippendorff, K., *Content Analysis: An introduction to its methodology.* 1980, London: Sage.
557. Denzin, N. and Y. Lincoln, *Handbook of qualitative research*. 2000: Sage: Thousand Oaks, CA. .
558. Riach, K., *Exploring Participant-centred Reflexivity in the Research Interview.* Sociology. , 2009. **43**(2): p. 356-370.

559. Richards, H. and C. Emslie, *The 'doctor' or the 'girl from the University'? Considering the influence of professional roles on qualitative interviewing.* Family Practice, , 2000. **Volume 17**(1): p. Pages 71–75.
560. Fontana, A. and J.H. Frey, *The Interview. From neutral stance to political involvement.* . The Sage Handbook of Qualitative Research., ed. N.K.a.L. In Denzin, Y.S. (editors). Vol. Third Edition. 2005: London: Sage. .
561. Mauthner, N.S. and A. Doucet, *Reflexive Accounts and Accounts of Reflexivity in Qualitative Data Analysis.* 2003. **37**(3): p. 413-431.
562. Barry, C.A., et al., *Using Reflexivity to Optimize Teamwork in Qualitative Research.* 1999. **9**(1): p. 26-44.
563. Mauthner, N.S., O. Parry, and K. Backett-Milburn, *The Data are Out there, or are They? Implications for Archiving and Revisiting Qualitative Data.* 1998. **32**(4): p. 733-745.
564. Beasant, L. and F. Sherratt, *Standard Operating Procedure (SOP) for the CONTRACT communication sub-study*. 2017.
565. Government document, *Data Protection Act* 1998, http://www.legislation.gov.uk/ukpga/1998/29/contents.
566. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.
567. Appleton, R.E., et al., *The use of MElatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS).* Health Technol Assess, 2012. **16**(40): p. i-239.
568. Atkinson, M., et al., *Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial.* Thorax, 2007. **62**(12): p. 1102-6.
569. Azzopardi, D.V., et al., *Moderate hypothermia to treat perinatal asphyxial encephalopathy.* N Engl J Med, 2009. **361**(14): p. 1349-58.
570. Balle, V., et al., *Treatment of children with secretory otitis media (SOM) with amoxicillin and clavulanic acid (Spektramox) or penicillin-V (Primcillin). Bacteriological findings in the nasopharynx before and after treatment.* Int J Pediatr Otorhinolaryngol, 1998. **45**(1): p. 77-82.
571. Craig, J.C., et al., *Antibiotic prophylaxis and recurrent urinary tract infection in children.* N Engl J Med, 2009. **361**(18): p. 1748-59.
572. Diabetes, C.C.T.R., Group., et al., *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.* N Engl J Med, 1993. **329**(14): p. 977-86.
573. UK Collaborative ECMO Trial Group, *UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation.* The Lancet, 1996. **348**(9020): p. 75-82.
574. Hissink Muller, P.C., et al., *A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study.* Pediatr Rheumatol Online J, 2017. **15**(1): p. 11.
575. Lenney, W., et al., *Management of Asthma in School age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety.* Health Technol Assess, 2013. **17**(4): p. 1-218.
576. Mitchell, C.D., et al., *Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical*

Research Council ALL97 randomized trial. Br J Haematol, 2005. **129**(6): p. 734-45.
577. Moreira, T.A., et al., *Combined oral midazolam-ketamine better than midazolam alone for sedation of young children: a randomized controlled trial.* Int J Paediatr Dent, 2013. **23**(3): p. 207-15.
578. Van Asperen, P.P., et al., *A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze.* J Paediatr Child Health, 1992. **28**(6): p. 442-6.
579. van Wijk, R.M., et al., *Helmet therapy in infants with positional skull deformation: randomised controlled trial.* BMJ, 2014. **348**: p. g2741.
580. Vora, A., et al., *Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial.* Lancet Oncol, 2013. **14**(3): p. 199-209.
581. Wake, M., et al., *Outcomes and costs of primary care surveillance and intervention for overweight or obese children: the LEAP 2 randomised controlled trial.* BMJ, 2009. **339**: p. b3308.
582. Wang, W.C., et al., *Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG).* Lancet, 2011. **377**(9778): p. 1663-72.
583. Ng, S.M., et al., *An explanatory randomised placebo controlled trial of levothyroxine supplementation for babies born <28 weeks' gestation: results of the TIPIT trial.* Trials, 2013. **14**: p. 211.
584. Cunningham, S., et al., *In search of the sample: recent experiences of a trial team in orthodontics.* Contemp Clin Trials, 2011. **32**(4): p. 530-4.
585. Levi, R.B., et al., *Diagnosis, disclosure, and informed consent: learning from parents of children with cancer.* J Pediatr Hematol Oncol, 2000. **22**(1): p. 3-12.
586. Allen, J., et al., *Is a randomised controlled trial of a maternity care intervention for pregnant adolescents possible? An Australian feasibility study.* BMC Med Res Methodol, 2013. **13**: p. 138.
587. Banks, J., et al., *Evaluating the transferability of a hospital-based childhood obesity clinic to primary care: a randomised controlled trial.* Br J Gen Pract, 2012. **62**(594): p. e6-12.
588. Bauchner, H., et al., *Therapy for acute otitis media. Preference of parents for oral or parenteral antibiotic.* Arch Pediatr Adolesc Med, 1996. **150**(4): p. 396-9.
589. Blickman, J.G., et al., *Child life services in pediatric radiology: A randomized controlled trial.* Pediatric Radiology, 2013. **43**: p. S573-S574.
590. Duncan, B., et al., *Parental perceptions of the therapeutic effect from osteopathic manipulation or acupuncture in children with spastic cerebral palsy.* Clin Pediatr (Phila), 2004. **43**(4): p. 349-53.
591. Forsander, G., *Family attitudes to different management regimens in diabetes mellitus.* Practical Diabetes International, 1995. **12**(2): p. 80-85.
592. Miner, J.R., et al., *Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain.* Acad Emerg Med, 2007. **14**(10): p. 895-8.
593. Payne, K., et al., *Day-case anaesthesia: What would the patient prefer?* Clinician in Management, 2004. **12**(3): p. 133-139.
594. Paediatric European Network for Treatment of AIDS (PENTA), *Parents' attitudes to their HIV-infected children being enrolled into a placebo-controlled*

trial: the PENTA 1 trial. Paediatric European Network for Treatment of AIDS. HIV Medicine, 1999. **1**: p. 25-31.
595. Rovers, M.M., et al., *The effect of ventilation tubes on language development in infants with otitis media with effusion: A randomized trial.* Pediatrics, 2000. **106**(3): p. E42.
596. Sandler, J., et al., *Effectiveness of 3 methods of anchorage reinforcement for maximum anchorage in adolescents: A 3-arm multicenter randomized clinical trial.* Am J Orthod Dentofacial Orthop, 2014. **146**(1): p. 10-20.
597. Sartain, S.A., et al., *Randomised controlled trial comparing an acute paediatric hospital at home scheme with conventional hospital care.* Arch Dis Child, 2002. **87**(5): p. 371-5.
598. Schuttelaar, M.L., et al., *A randomized controlled trial in children with eczema: nurse practitioner vs. dermatologist.* Br J Dermatol, 2010. **162**(1): p. 162-70.
599. Sederberg-Olsen, J., et al., *Problems in recruiting patients to controlled trials on children with secretory otitis media: a demographic comparison of excluded versus included patients.* Int J Pediatr Otorhinolaryngol, 1998. **43**(3): p. 229-33.
600. Spandorfer, P.R., et al., *Oral versus intravenous rehydration of moderately dehydrated children: a randomized, controlled trial.* Pediatrics, 2005. **115**(2): p. 295-301.
601. Tercyak, K.P., Jr., et al., *Offering a randomized trial of intensive therapy for IDDM to adolescents. Reasons for refusal, patient characteristics, and recruiter effects.* Diabetes Care, 1998. **21**(2): p. 213-5.
602. Willey, S.E., D.M. Griffiths, and J.J. Nightingale, *Prospective randomised controlled trial comparing rectal versus oral paracetamol and diclofenac in children following appendicectomy.* Acute Pain, 2005. **7**(1): p. 33-35.
603. Williams, K.G., et al., *A randomized controlled trial of cast versus splint for distal radial buckle fracture: an evaluation of satisfaction, convenience, and preference.* Pediatr Emerg Care, 2013. **29**(5): p. 555-9.
604. Wright, J.G., et al., *Treatments for paediatric femoral fractures: a randomised trial.* Lancet, 2005. **365**(9465): p. 1153-8.
605. Wynn, L., et al., *Recruitment of infants with sickle cell anemia to a Phase III trial: data from the BABY HUG study.* Contemp Clin Trials, 2010. **31**(6): p. 558-63.
606. Young, B.J., et al., *Pretreatment attrition and childhood social phobia: Parental concerns about medication.* J Anxiety Disord, 2006. **20**(8): p. 1133-47.
607. Gowers, S.G., et al., *A randomised controlled multicentre trial of treatments for adolescent anorexia nervosa including assessment of cost-effectiveness and patient acceptability - the TOuCAN trial.* Health Technol Assess, 2010. **14**(15): p. 1-98.
608. Paradise, J.L., et al., *Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials.* N Engl J Med, 1984. **310**(11): p. 674-83.
609. Paradise, J.L., et al., *Efficacy of adenoidectomy for recurrent otitis media in children previously treated with tympanostomy-tube placement. Results of parallel randomized and nonrandomized trials.* JAMA, 1990. **263**(15): p. 2066-73.

610. Reddihough, D.S., et al., *Efficacy of programmes based on Conductive Education for young children with cerebral palsy.* Dev Med Child Neurol, 1998. **40**(11): p. 763-70.
611. Rovers, M.M., et al., *Generalisability of clinical trials in otitis media with effusion.* Int J Pediatr Otorhinolaryngol, 2001. **60**(1): p. 29-40.
612. van Wijk, R.M., et al., *Parents' decision for helmet therapy in infants with skull deformation.* Childs Nerv Syst, 2014. **30**(7): p. 1225-32.
613. Mattila, P.S., et al., *Prevention of otitis media by adenoidectomy in children younger than 2 years.* Arch Otolaryngol Head Neck Surg, 2003. **129**(2): p. 163-8.
614. Weinstein, S.L., et al., *Effects of bracing in adolescents with idiopathic scoliosis.* N Engl J Med, 2013. **369**(16): p. 1512-21.
615. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* BMJ, 2009. **339**: p. b2535.
616. Rovers, M.M., et al., *Generalizability of trial results based on randomized versus nonrandomized allocation of OME infants to ventilation tubes or watchful waiting.* J Clin Epidemiol, 2001. **54**(8): p. 789-94.
617. Dixon-Woods, M., et al., *Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups.* BMC Med Res Methodol, 2006. **6**: p. 35.
618. Sandelowski, M., S. Docherty, and C. Emden, *Focus on qualitative methods. Qualitative metasynthesis: issues and techniques.* Res Nurs Health, 1997. **20**(4): p. 365-71.
619. Walter, S., et al., *Beyond the treatment effect: Evaluating the effects of patient preferences in randomised trials.* Stat Methods Med Res, 2014. **26**(1): p. 489-507.
620. Schulz, K.F., et al., *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* Trials, 2010. **11**: p. 32.
621. Moher, D., et al., *CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c869.
622. Wulf, F., Krasuska, M. and Bullinger, M. , *Determinants of decision-making and patient participation in paediatric clinical trials: A literature review.* Open Journal of Pediatrics, 2012. **2**: p. 1-17.
623. Snethen, J.A., et al., *Family patterns of decision-making in pediatric clinical trials.* Res Nurs Health, 2006. **29**(3): p. 223-32.
624. Lees, A., et al., *Positioning Children's Voice in Clinical Trials Research: A New Model for Planning, Collaboration, and Reflection.* Qual Health Res, 2017. **27**(14): p. 2162-2176.
625. Ashcroft, R., et al., *Children's consent to research participation: social context and personal experience invalidate fixed cutoff rules.* Am J Bioeth, 2003. **3**(4): p. 16-8.
626. Siminoff, L.A., J.H. Fetting, and M.D. Abeloff, *Doctor-patient communication about breast cancer adjuvant therapy.* J Clin Oncol, 1989. **7**(9): p. 1192-200.
627. Centre for Reviews and Dissemination *Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care*. 2009. DOI: 97811900640473.
628. Harman, N., et al., *Development of an online resource for recruitment research in clinical trials (ORRCA).* Trials. , 2015. **16(Suppl 2):98.**

629. Selva, A.S.I., et al., *Development and use of a content search strategy for retrieving studies on patients' views and preferences.* Health Qual Life Outcomes., 2017. **Aug 30;15(1):126**.
630. van Hoorn, R., et al., *The development of PubMed search strategies for patient preferences for treatment outcomes.* BMC Med Res Methodol, 2016. **16**: p. 88.
631. Galton, F., *Regression towards mediocrity in hereditary stature. .* Journal of the Anthropological Institute 1886. **15**: p. 246-63.
632. Morton, V. and D.J. Torgerson, *Effect of regression to the mean on decision making in health care.* BMJ, 2003. **326**(7398): p. 1083-4.
633. O'Cathain A, T.K., Rudolph A, Drabble SJ, Hewison J. , *What can qualitative research do for randomised controlled trials? A systematic mapping review.* BMJ Open 2013;3:e002889., 2013.
634. Alliance for Clinical Trials in Oncology, *A Randomized Trial of Radical Prostatectomy Versus Brachytherapy for Patients With T1c or T2a N0 M0 Prostate Cancer*. 2001.
635. NCIC Clinical Trials Group, *A Phase III Study of Active Surveillance Therapy Against Radical Treatment in Patients Diagnosed With Favourable Risk Prostate Cancer [START]*. 2007.
636. Crook, J.M., et al., *Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial.* J Clin Oncol, 2011. **29**(4): p. 362-8.
637. Wilt, T.J., et al., *Radical prostatectomy versus observation for localized prostate cancer.* N Engl J Med, 2012. **367**(3): p. 203-13.
638. Schandelmaier, S., et al., *Premature Discontinuation of Pediatric Randomized Controlled Trials: A Retrospective Cohort Study.* J Pediatr, 2017. **184**: p. 209-214 e1.
639. Wade, J., et al., *How informed is your consent? Techniques to facilitate informed consent in trial recruitment [abstract].* in *Clin Trials, 2010*. 2010.
640. Avery, K.N.L.M., C.; Berrisford R.; Barham C, Donovan, J.L.; Elliott, J.; Falk, S.J.; Goldin, R.; Hanna, G.; Hollowood, A.; Krysztopik, R.; Noble, S.; Sanders, G.; Streets, CG.; Titcomb, DR.; Wheatley, T.; Blazeby, J.M., *The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer - the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial.* Trials., 2014. **Jun 2;**(15:): p. 200.
641. Townsend, D., et al., *A systematic review of training programmes for recruiters to randomised controlled trials.* Trials, 2015. **16**(1): p. 432.
642. Mills, N., et al., *Training health professionals to recruit into challenging randomized controlled trials improved confidence: the development of the QuinteT randomized controlled trial recruitment training intervention.* J Clin Epidemiol, 2018. **95**: p. 34-44.
643. Lane, J.A., et al., *Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial.* Lancet Oncol, 2014. **15**(10): p. 1109-18.
644. Bradley, C., *Designing medical and educational intervention studies. A review of some alternatives to conventional randomized controlled trials.* Diabetes Care, 1993. **16**(2): p. 509-18.

645. Feine, J.S., M.A. Awad, and J.P. Lund, *The impact of patient preference on the design and interpretation of clinical trials.* Community Dent Oral Epidemiol, 1998. **26**(1): p. 70-4.
646. Sammons, H.M., et al., *British and Canadian views on the ethics of paediatric clinical trials.* Eur J Clin Pharmacol, 2007. **63**(5): p. 431-6.
647. Kerr, C.E.P., et al., *The impact of describing clinical trial treatments as new or standard.* Patient Education and Counseling, 2004. **53**(1): p. 107-113.
648. Adamson, S.J., D.J. Sellman, and G.M. Dore, *Therapy preference and treatment outcome in clients with mild to moderate alcohol dependence.* Drug Alcohol Rev, 2005. **24**(3): p. 209-16.
649. Ananworanich, J., et al., *A feasibility study of immediate versus deferred antiretroviral therapy in children with HIV infection.* AIDS Res Ther, 2008. **5**: p. 24.
650. Byrnes, H.F., et al., *Implementation fidelity in adolescent family-based prevention programs: relationship to family engagement.* Health Educ Res, 2010. **25**(4): p. 531-41.
651. George, S.Z. and M.E. Robinson, *Preference, expectation, and satisfaction in a clinical trial of behavioral interventions for acute and sub-acute low back pain.* J Pain, 2010. **11**(11): p. 1074-82.
652. Aalborg, A.E., et al., *Implementation of adolescent family-based substance use prevention programs in health care settings: Comparisons across conditions and programs.* Health Educ J, 2012. **71**(1): p. 53-61.
653. Bishop, M.D., et al., *The influence of clinical equipoise and patient preferences on outcomes of conservative manual interventions for spinal pain: an experimental study.* J Pain Res, 2017. **10**: p. 965-972.
654. Kearney, A., et al., *Reducing attrition within clinical trials: The communication of retention and withdrawal within patient information leaflets.* PLoS One, 2018. **13**(10): p. e0204886.
655. Thompson, E.A., et al., *The feasibility of a pragmatic randomised controlled trial to compare usual care with usual care plus individualised homeopathy, in children requiring secondary care for asthma.* Homeopathy, 2011. **100**(3): p. 122-30.
656. Hissink Muller, P.C.E., et al., *Participation in a single-blinded pediatric therapeutic strategy study for juvenile idiopathic arthritis: are parents and patient-participants in equipoise?* BMC Med Ethics, 2018. **19**(1): p. 96.
657. Anderson, E., et al., *Testing the feasibility of recruiting adolescents with CFS/ME to Internet-delivered therapy: Internal pilot within a randomised controlled trial investigating online Cognitive Behavioural Therapy (Fatigue In Teenagers on the interNET in the NHS – "FITNET-NHS") compared to Skype-delivered Activity Management for adolescents with CFS/ME.* [draft October 2019].
658. Brigden, A., *Results of the feasibility phase of the Managed Activity Graded Exercise iN Teenagers and Pre-Adolescents (MAGENTA) Randomised Controlled Trial of treatments for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis.* Pilot and Feasibility Studies, [submitted for publication August 2019].
659. Hall, N.J., et al., *CONservative TReatment of Appendicitis in Children – a randomised controlled Trial – CONTRACT (Feasibility study)*. [Submitted 2019].

660. Eborall, H.C., et al., *The face of equipoise--delivering a structured education programme within a randomized controlled trial: qualitative study.* Trials, 2014. **15**: p. 15.
661. Spillane, A.J. and G.B. Mann, *Surgeon knows best versus breast cancer surgical clinical trial equipoise: a plea for the sake of future trials.* ANZ J Surg, 2017. **87**(3): p. 111-112.
662. Radley, A. and M. Billig, *Accounts of health and illness: Dilemmas and representations.* Sociology of Health & Illness, 1996. **18**(2): p. 220-240.
663. May, V., *On being a 'good' mother: The moral presentation of self in written life stories.* Sociology-the Journal of the British Sociological Association, 2008. **42**(3): p. 470-486.
664. Comwell, J., *Hard-Eamed Lives: Accounts of Health and Illness from East London*. 1984, London: Tavistock.
665. Nelson, P.A., et al., *'Doing the "right" thing': how parents experience and manage decision-making for children's 'normalising' surgeries.* Soc Sci Med, 2012. **74**(5): p. 796-804.
666. Lock, C., et al., *Childhood tonsillectomy: who is referred and what treatment choices are made? Baseline findings from the North of England and Scotland Study of Tonsillectomy and Adenotonsillectomy in Children (NESSTAC).* Arch Dis Child, 2010. **95**(3): p. 203-8.
667. Blair, R.L., et al., *The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society.* J Laryngol Otol, 1996. **110 Suppl 20**: p. 1-25.
668. Ellington, M., Jr., et al., *Child health status, neurodevelopmental outcome, and parental satisfaction in a randomized, controlled trial of nitric oxide for persistent pulmonary hypertension of the newborn.* Pediatrics, 2001. **107**(6): p. 1351-6.
669. Plank, R.M., et al., *A randomized trial of Mogen clamp versus Plastibell for neonatal male circumcision in Botswana.* J Acquir Immune Defic Syndr, 2013. **62**(5): p. e131-7.
670. Janevic, M.R., et al., *The role of choice in health education intervention trials: a review and case study.* Soc Sci Med, 2003. **56**(7): p. 1581-94.
671. Locock, L. and L. Smith, *Personal benefit, or benefiting others? Deciding whether to take part in clinical trials.* Clin Trials, 2011. **8**(1): p. 85-93.
672. Brigden, A., et al., *How are behavioural interventions delivered to children (5-11-year olds): A systematic mapping review.* BMJ Paediatrics Open, 2019 [In press].
673. Reilly, K.C., et al., *"C.H.A.M.P. Families": Description and Theoretical Foundations of a Paediatric Overweight and Obesity Intervention Targeting Parents-A Single-Centre Non-Randomised Feasibility Study.* Int J Environ Res Public Health, 2018. **15**(12).
674. Ng, C.Y., et al., *Theory-Based Health Behavior Interventions for Pediatric Chronic Disease Management: A Systematic Review.* JAMA Pediatr, 2018. **172**(12): p. 1177-1186.
675. Michie, S., et al., *Developing and Evaluating Digital Interventions to Promote Behavior Change in Health and Health Care: Recommendations Resulting From an International Workshop.* J Med Internet Res, 2017. **19**(6): p. e232.
676. Miller, V.A., C. Feudtner, and A.F. Jawad, *Children's Decision-Making Involvement About Research Participation: Associations With Perceived*

Fairness and Self-Efficacy. J Empir Res Hum Res Ethics, 2017. **12**(2): p. 87-96.
677. Bandura, A., *Health promotion by social cognitive means.* Health Educ Behav, 2004. **31**(2): p. 143-64.
678. Weinger, K., K.A. O'Donnell, and M.D. Ritholz, *Adolescent views of diabetes-related parent conflict and support: a focus group analysis.* J Adolesc Health, 2001. **29**(5): p. 330-6.
679. Dixon-Woods, M., B. Young, and D. Heney, *Partnerships with children.* BMJ, 1999. **319**(7212): p. 778-80.
680. Mays, N. and C. Pope, *Rigour and qualitative research.* BMJ, 1995. **311**(6997): p. 109-12.
681. O'Cathain A, T.K., Drabble SJ, Rudolph A, Goode J, Hewison J., *Maximising the value of combining qualitative research and randomised controlled trials in health research: the QUAlitative Research in Trials (QUART) study – a mixed methods study. .* Health Technol Assess. , 2014. **Jun; 18**((38):): p. 1-197. .
682. Liaschenko, J. and S.M. Underwood, *Children in Research: Fathers in Cancer Research—Meanings and Reasons for Participation.* Journal of Family Nursing, 2001. **7**(1): p. 71-91.
683. Macfadyen, A., et al., *Involving fathers in research.* 2011. **16**(3): p. 216-219.
684. Swallow, V., et al., *Fathers and mothers developing skills in managing children's long-term medical conditions: how do their qualitative accounts compare?* Child Care Health Dev, 2011. **37**(4): p. 512-23.
685. Murphy, E. and R. Dingwall, *Qualitative Methods and Health Policy Research*. 2003, New York: Walter de Gruyter, Inc.
686. Rowlands, C., et al., *Detailed systematic analysis of recruitment strategies in randomised controlled trials in patients with an unscheduled admission to hospital.* BMJ Open, 2018. **8**(2).
687. Leira, E.C., et al., *Extending acute trials to remote populations: a pilot study during interhospital helicopter transfer.* Stroke, 2009. **40**(3): p. 895-901.
688. Gillies, K., et al., *Systematic Techniques to Enhance rEtention in Randomised controlled trials: the STEER study protocol.* Trials, 2018. **19**(1): p. 197.
689. Kukla, R., *Conscientious autonomy: displacing decisions in health care.* Hastings Cent Rep, 2005. **35**(2): p. 34-44.
690. Gonzalez, K.W., et al., *Understanding parental refusal of permission for child participation in surgical prospective trials.* Pediatr Surg Int, 2016. **32**(5): p. 505-8.
691. Jenkins, V., et al., *Discussing randomised clinical trials of cancer therapy: evaluation of a Cancer Research UK training programme.* BMJ, 2005. **330**(7488): p. 400.
692. Blazeby, J., et al., *Optimising recruitment into RCTs in surgery. A focused workshop*. 2015, University of Bristol. .

Appendices

Appendix 1: Ethical Approvals

Ethical approval for my PhD project incorporating qualitative data from all four trials was obtained via the Research and Enterprise Development (RED) Team University of Bristol, (Study 2374). All work was undertaken with the financial support of the MRC ConDuCT-II (**C**ollaboration and innovation for **D**ifficult and **C**omplex randomised controlled **T**rials **I**n **I**nvasive procedures) Hub for Trials Methodology Research (MR/K025643/1). Good Clinical Practice (GCP) training, Disclosure and Barring Service (DBS formerly CRB) checks, research passports and local NHS letters of access were also obtained for each qualitative study within each trial.

Overall trial findings from the MAGENTA, FITNET-NHS and CONTRACT RCTs were not known to me at the time of writing this thesis. Findings from the SMILE RCT were published in July 2017.

Ethical approval was obtained for each RCT as detailed below:

Study name and acronym: Specialist Medical Intervention & Lightning Evaluation: SMILE

Ethics committee: South West 2 Local Research Ethics Committee

REC reference: 10/H0206/32

Approval granted: 8th September 2010

Study name and acronym: Managed Activity Graded Exercise in Teenagers and Pre-Adolescents: MAGENTA

Ethics committee: NRES Committee South West – Frenchay

REC reference: 15/SW/0124

Approval granted: Feasibility: REC: 3rd July 2015. NHS Trust: 13th August 2015

The response to a letter of enquiry about the MAGENTA study from an MP, a letter to the ethics committee concerning this, and the ethics committee's re-review of MAGENTA and confirmed favourable opinion were published online at: http://www.bristol.ac.uk/ccah/research/childdevelopmentdisability/chronic-fatigue/magenta-trial/ethics/

Study name and acronym: Investigating the effectiveness and cost-effectiveness of using FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to activity management to treat CFS/ME in the United Kingdom: FITNET-NHS

Ethics committee: South West Frenchay Research Ethics committee

REC reference: 16/SW/0268

Approval granted: REC: 10th October 2016 HRA:13th October 2016

Study name and acronym: CONservative TReatment of Appendicitis in Children a randomised controlled Trial: CONTRACT

Ethics committee: South Central Hampshire A Research Ethics Committee

REC reference: 16/SC/0596

Approval granted: 22 November 2016

Appendix 2: Systematic Review

Eligibility and Inclusion Criteria

Participants/population:

Inclusion: Children and young people aged 0 – 17.99yrs at trial entry.

Exclusion: adult RCT participants aged 18 plus.

Interventions:

Inclusion: Any intervention, combination of interventions.

Exclusion: None.

Comparators:

Inclusion: Any comparative intervention.

Exclusion: None.

Outcomes:

Inclusion: Any clinical outcome, this review is not seeking to review clinical outcome, instead it will review the expressed treatment preferences of children, young people and their parents in relation to their randomisation allocation. Include if 'Preference' for treatment group is reported by patient/parent before or after randomisation/intervention, this could be expressed as preference for one or more treatment groups in relation to allocation and/or treatment/outcome OR a 'non-preference' or dislike for particular treatment group(s).

Exclusion: If 'Satisfaction' is reported by patient/parent after randomisation/intervention, it is satisfaction with outcome/a received treatment NOT a ‘preference’ between treatment groups. Use reasons: 'Reports patient OR parent satisfaction with treatment outcome’.

Context:

Inclusion: The first RCT paper was published in 1948, therefore database searches will be limited to the time period 1950-2014 inclusive.

Exclusion: Any study prior to the year 1950.

Study design:

Inclusion: RCTs with prospectively recruited children and young people where there is randomisation including, (complete or partial) and treatment preference is reported for all, (or some) of the participants. Qualitative studies that report treatment preference in RCTs.

Exclusion: Non-randomised studies, (e.g. observational, quasi-randomised).

MEDLINE Search Strategy

Database: Medline 1950 to present

Search Strategy:

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1 adolescent/ or exp child/ (2516113)

2 minors/ (2367)

3 Pediatrics/ (42050)

4 (pediatri$ or paediatri$ or teenager$ or young person$ or young people).ti,ab. (245419)

5 (adolesc$ or boy$ or girl$ or child$ or juvenil$ or schoolchild$).ti,ab. (1213948)

6 or/1-5 (2862052)

7 (exp adult/ or adult.ti.) not (pediatri$ or paediatri$ or teenager$ or adolesc$ or young person$ or young people or boy$ or girl$ or child$ or juvenil$ or schoolchild$).ti,ab. (5590793)

8 6 not 7 (1740500)

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9 exp Clinical Trials as Topic/ (295653)

10 ((random* or crossover* or control* or cross-sectional or observational or longitudinal or clinical) adj4 (trial or trials or design or study or studies)).ti,ab. (1026721)

11 9 or 10 (1187255)

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12 ((patient$ or participant$ or parent$ or mother$ or father$ or child$ or carer$ or caregiver$ or care-giver$ or personal) adj3 (view or views or priorit$ or perception$ or prefer$ or belief$ or expectation$ or choice$ or perspective$ or satisfact$ or experience or experiences or opinion$ or concern or concerns or feeling$)).ti,ab. (189786)

13 exp patient satisfaction/ (65985)

14 professional-family relations/ or professional-patient relations/ or physician-patient relations/ or researcher-subject relations/ (97784)

15 12 or 13 or 14 (312317)

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16 8 and 11 and 15 (6445)

---

17 letter/ (857062)

18 editorial/ (358231)

19 news/ (165244)

20 exp historical article/ (333331)

21 Anecdotes as topic/ (4682)

22 comment/ (581752)

23 case report/ (1739336)

24 (letter or comment$).ti. (91081)

25 or/17-24 (3403060)

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26 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (848254)

27 25 not 26 (3371992)

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28 animals/ not humans/ (4004886)

29 exp Animals, Laboratory/ (764211)

30 exp Animal Experimentation/ (6725)

31 exp Models, Animal/ (447357)

32 exp rodentia/ (2802604)

33 (rat or rats or mouse or mice).ti. (1119422)

34 or/27-33 (7983465)

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35 16 not 34 (6323)

Medline search carried out 6th January 2015 retrieved 6323 records

EMBASE 8th January 2015 retrieved 9296 records

CINHAL 13th January 2015 retrieved 1977 records

Cochrane 26th January 2015 5853 records

After deduplication:

MEDLINE = 4813

EMBASE = 5204

CINAHL = 1824

COCHRANE = 5094

References imported for screening in Covidence: 16935

Title and abstract screening: Inclusion criteria

1. FACTOR/ASSESSMENT 1. a. Published 1950 –2014? (y/n)
2. FACTOR/ASSESSMENT 1. b. RCT (y/n/unclear)
3. FACTOR/ASSESSMENT 2. Age? (add age range)
4. FACTOR/ASSESSMENT 3a. Reports TP quantitative? (y/n)
5. FACTOR/ASSESSMENT 3b. Reports TP qualitative? (y/n)
6. FACTOR/ASSESSMENT 3c. Reports TP descriptively? (y/n)
7. COVIDENCE REASONS FOR EXCLUSION

Include/Exclude:

a. Wrong study design
b. Adult population
c. Wrong patient population
d. Reports patient OR parent satisfaction with treatment outcome not preference between intervention groups
e. No discussion of preference between intervention groups
f. study protocol & no indication that treatment preference between groups will be measured
g. study protocol & hand search will be carried out for full trial results paper
h. Full text not available
i. Duplicate
j. Abstract or poster & hand search will be carried out on author for full publication(s) in relation to trial
k. Data analysis not separated by age for those under/over 18yrs
l. Any additional comments? e.g. type of preference reported

Data extraction fields

Data extraction fields:
Author
Primary outcome or secondary paper
Country
RCT type (full, feasibility, preference, comprehensive cohort)
RCT aim
Area of study & Description of interventions
Participant age (months/years)
Is preference expressed by patient/parent prior to randomisation
Is preference expressed by patients (in addition to parents)
Number of eligible participants consenting to randomised groups
Number of eligible patients not randomised because of treatment preference n (%)
Post randomisation drop-out due to preference
Total: withdrawn/discontinued treatment/crossed over/lost to follow up
Further information reported on preference (included: preference of parent different from young person, preference groups added, early trial closure, extension required and trial terminated early)
Additional qualitative data extraction fields:
Number of qualitative participants (parents/ participants)
Qualitative aim
Qualitative data collection method(s)
Qualitative approach & data analyses

CASP: Critical Appraisal Skills Program

10 questions to help you make sense of qualitative research

How to use this appraisal tool

Three broad issues need to be considered when appraising a qualitative study:

Are the results of the study valid?	(Section A)
What are the results?	(Section B)
Will the results help locally?	(Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.:

Critical Appraisal Skills Programme (2017). CASP (insert name of checklist i.e. Qualitative Research) Checklist. [online] Available at: *URL*. Accessed: *Date Accessed*.

Example: meta-ethnography – second order constructs

Seven themes with no preference related data: 2nd order constructs (themes) Caldwell 2003.

NO PREF DATA [Themes] 2nd order		
Caldwell_2003		
Parental Factors - Parents' Beliefs and Knowledge	0	0
Parental Factors - Parents' Emotional Response to Trials	0	0
Child Factors - Children's Choices	0	0
Child Factors - Child's Condition	0	0
Trial Factors - Trial Uncertainty	0	0
Trial Factors - Doctor Factors	0	0
Parents' Suggestions - Aids for Decision-Making	0	0

Five themes with preference related data: 2nd order constructs (themes) and author's interpretation and theory, Caldwell 2003.

PREF DATA [Themes] 2nd order		
Caldwell_2003		
Gains-risk balance - Perceived Benefits	1	1
Gains-risk balance - Perceived Risks	1	1
Trial Factors - Placebo-Controlled Trials Versus Active Trials	1	1
Parents' Suggestions - Improved Communication	1	1
Increasing Incentives and Decreasing Disincentives	1	1
Author(s) interpretation & theory CALDWELL	1	2

Translation of first, (participant quotations) second, (authors' themes) to third order (synthesised) construct

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Allmark_2006	*"I remember saying to him..."Oh great, great, like some effing placebo'' is what I said to him; so, no, I totally understood that idea, so I was kind of glad [because the baby received cooling]" [Mother: 4]*	Randomisation	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment
Byrne-Davis_2010	*"we were slightly disappointed that [...] he got regimen A but of course the flip side of the coin is if he gets away with it and he avoids a much more toxic you know regimen then fantastic"*	How Recruitment Felt to the Parents: Parents understood the purpose of the trial	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Assimilating new information with pre-existing knowledge
Byrne-Davis_2010	*"he [the doctor] was saying, you know "you've got to balance out the low risk here to the high intensity here". Does that balance out? And with her having the [name of serious infection], um, do we really want to put her at risk from being susceptible to those sort of things again when, maybe, she doesn't really - in the bracket that she's in, where it is a 85%, 95% cure rate - do we need to put her in that thing"*	How Recruitment Felt to the Parents: Parents understood the purpose of the trial	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT: Assimilating new information with pre-existing knowledge
Byrne-Davis_2010	*"the computer makes the decision [...] and I just think, they give you all this information and then, you know, randomisation is just purely you're picked at random, it's a lottery. It's er, yeah, I think they should have certain criteria, that maybe if you fit these specific criterias, or if you have a daughter that's fifteen years of age, or twelve years or whatever, a reason for it, or a reason for you not going on it would probably be better rather than just saying 'oh well, the computer picks and that's it.'"*	How Recruitment Felt to the Parents: Parents appeared to understand equipoise, voluntariness and randomisation	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT: Understanding of trial processes (nature of RCT, randomisation, equipoise)
Byrne-Davis_2010	*"if there was a hope that he would get better treatment then at least we felt like we'd done everything that we could [...] if the worst did happen if we'd said regimen A and then he didn't make it I would... I would have always thought what if we'd have done regimen C, would it have made a difference and I think we needed to know that we'd done everything we possibly could"*	How Recruitment Felt to the Parents: Parents appeared to understand equipoise, voluntariness and randomisation	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and responsibility
Byrne-Davis_2010	*"very difficult for me to say, yes, he could just have one [intensive block]"... "in the back of my mind I can't let go of the thought that two intensive periods is better than one"*	How Recruitment Felt to the Parents: Parents appeared to understand equipoise, voluntariness and randomisation	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and responsibility
Byrne-Davis_2010	*"gut reaction" [to] "give him more chemotherapy"*	How Recruitment Felt to the Parents: Parents appeared to understand equipoise, voluntariness and randomisation	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Assimilating new information with pre-existing knowledge

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Caldwell_2003	*"...the most important thing I found was being treated like an intelligent person...if it is explained to people...you are more likely to get a positive sort of response [...] if...I didn't know anything at all about trials, I'd be thinking trials to me sound experimental, placebo to me sounds like it's not a real drug. ...it all depends on how it's been worded and how it's been explained..."*	Parents' Suggestions: Improved Communication	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of treatment groups and unanswered questions
Caldwell_2003	*"They might get the new drugs that work.."*	Gains-risk balance: Perceived Benefits	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Caldwell_2003	*"...it's a worry thinking you're doing the wrong thing...people don't want to...(be) the one being responsible once again."*	Gains-risk balance: Perceived Benefits	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and responsibility (A difficult decision)
Caldwell_2003	*"He would be peeved off if he got the jelly beans...he would want the real thing..."*	Trial Factors: Placebo-Controlled Trials Versus Active Trials	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Caldwell_2003	*"...that's just like going to the doctor and them saying well we are just not going to treat this child."*	Trial Factors: Placebo-Controlled Trials Versus Active Trials	An emotional response to randomisation and expressions of preference for treatment: Disappointment and Anger
Caldwell_2003	*"...I was at the end of my rope...if it was the placebo, well that means that we can try the real thing anyway."*	Parents' Suggestions: Increasing Incentives and Decreasing Disincentives	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Hopes
Carvalho_2013	*"I have talked to God because He knows what is best for him, doesn't He?" [Mother's expectation prior to randomisation: Sedation. Group assigned: Physical restraint]*	Mothers' feelings before and after the drawing	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fate
Carvalho_2013	*"So in this case there is no choice? Is it by lot?" [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Sedation]*	Vulnerability to the randomisation process	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Carvalho_2013	*"Just one question: Why can't we choose?... . . Oh, I would not want [to do it]. I came here with my heart in my hand thinking about it. I thought I could choose to come here and say 'I do not want general anesthesia.' The doctor at the health center had already said that a sedative might be necessary, so I was already thinking 'I will not allow it." [Mother's expectation prior to randomisation: Physical restraint. Group assigned: General anesthesia]*	Vulnerability to the randomisation process	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Carvalho_2013	*"[Son,] take one, which one do you want? Just take one, stick your finger in here and take it." [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Sedation]*	Vulnerability to the randomisation process	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility / Fate and Luck
Carvalho_2013	*"At the beginning I was scared, we just get scared, I was scared." [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Physical restraint]*	Mothers' feelings before and after the drawing: pre-drawing responses	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Carvalho_2013	*"Oh, fear of what I want not happening." [Mother's expectation prior to randomisation: General anesthesia. Group assigned: General anesthesia]*	Mothers' feelings before and after the drawing: pre-drawing responses	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Carvalho_2013	*It cannot continue the way it is. I am like really afraid of general anesthesia, but, as others say, if it is necessary, what can I do? . . . As I am receiving the treatment for free I accept what we get. And I have no choice." [Mother's expectation prior to randomisation: Sedation. Group assigned: Sedation]*	Mothers' feelings before and after the drawing: pre-drawing responses	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears (Access to treatment)

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Carvalho_2013	*"Relieved. I feel like jumping for joy. That is great." [kisses the child] [laughs] [Mother's expectation prior to randomisation: Sedation. Group assigned: Sedation]*	Mothers' feelings before and after the drawing: after the drawing	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Relief and Happiness
Carvalho_2013	*"We feel relief, knowing he will not feel the treatment so much." [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Sedation]*	Mothers' feelings before and after the drawing: after the drawing	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Relief
Carvalho_2013	*"We would like to have gotten the general anesthesia . . . Now we have to do it with the sheet [passive restraint]." [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Physical restraint]*	Mothers' feelings before and after the drawing: after the drawing	An emotional response to randomisation and expressions of preference for treatment: Disappointment
Carvalho_2013	*"Oh, no!" [Mother's expectation prior to randomisation: Physical restraint. Group assigned: General anesthesia]*	Mothers' feelings before and after the drawing: after the drawing	An emotional response to randomisation and expressions of preference for treatment: Disappointment
Carvalho_2013	*no quotation [Mother cried] [Mother's expectation prior to randomisation: General anesthesia. Group assigned: Physical restraint]*	Mothers' feelings before and after the drawing: after the drawing	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Disappointment
Eiser_2005	*"we would have wanted the old one but if it helps others it's OK. They pick you at random and we got picked (for the new drug)". [new treatment/negative]*	Preference for different arms of the trial	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Disappointment
Eiser_2005	*"We were glad to get the old treatment. It means if she relapses we can still have the new treatment" [standard treatment/positive]*	Preference for different arms of the trial	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Relief
Eiser_2005	*"We are not bothered about being on the old treatment as they only give the best, don't they?" [standard treatment/positive]*	Preference for different arms of the trial	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Eiser_2005	*"Treatment is excellent anyway and anything they offer can only be better. I am all for research" [new treatment/positive]*	Preference for different arms of the trial	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Fears
Eiser_2005	*"We were disappointed. You go through all that talking and decision making and then you get the old treatment anyway"*	Understanding of the trial: Aims and Randomisation	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Disappointment
Eiser_2005	*"I can't remember what it was about. Was it we could choose whether it was one drug we had or another, or whether we could be put in a trial and then the people running the trial would choose the drug for us and then we wouldn't know which we were on? We agreed but were not happy about the computer deciding"*	Understanding of the trial: Aims and Randomisation	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise)
Glogowska_2001	*"I was told yes, he had a problem and he needed help and I think now, well, I've got to wait ... to get any help"*	Parents understanding of the nature of the trial	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Disappointment (Access to treatment)
Glogowska_2001	*"It was a case of if his name came out of the box ... then he was lucky enough to go on it ... which I think is wrong ... but then I suppose it's all the cutbacks"*	Parents understanding of the nature of the trial	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise) Fate and luck
Glogowska_2001	*"If she'd [the therapist] seen something ... and thought ... this is something really serious well then he wouldn't have been put on that sort of waiting group."*	Parents' motivation for taking part	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT (Access to treatment)
Glogowska_2001	*"I don 't mind answering the questions ... and assessing him ... but it's just the fact ... I wish it was ... therapy a lot more"*	Parents' motivation for taking part	An emotional response to randomisation and expressions of preference for treatment: Vulnerability, Hopes and Disappointment (Access to treatment)
Glogowska_2001	*"I couldn't justify saying O.K. we'll go along with this research group and wait for a year because he needed help then"*	The meaning of participation to the parents	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility (Access to treatment)

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Jollye_2009	*"You associate a blood transfusion with someone being sick, really sick." [blood transfusion trial]*	Contemplating the research trial - risks and benefits	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility (Understanding of treatment groups)
Jollye_2009	*[child might not be randomised to the] "right" arm [Ventilation trial]*	Contemplating the research trial - risks and benefits	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Lock_2010	*"If it come to the 10 month up and he didn't need it done, my wife says, 'Oh I might get it done anyway, just in case"*	Management of recurrent sore: Having a tonsillectomy 'just in case'	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Management of condition and practical implications
Lock_2010	*"Yeah his brother had his took out and he's been brilliant since he got his done … it was the best thing I could have done for him … that's why we are trying to push to get his done because it's just recurring all the time, every couple of months or so and it's not fair on the bairn and it's not fair on his education either because he's having to have the time off school because he's just, well he wouldn't be any good at school"*	Management of recurrent sore: Using the experience of other & Requesting tonsillectomy	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Perceived benefits and risks (Management of condition & practical implications).
Shilling_2011	*"Her only real way of getting it is to go and take part in the trial because then, I've got sort of a 50/50 chance of either she gets the drug or she gets the placebo. But she wouldn't be getting it otherwise"*	Communication as observed - Mismatches and misunderstandings	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Perceived benefits and risks (Access to treatment medication or therapy)
Shilling_2011	*"getting the right medication"* *Doctor: "So we are running this study for the last year now, where I'm afraid half the [babies] get the supplement and half the [babies] doesn't get it"*	Communication as observed - Mismatches and misunderstandings	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Shilling_2011	*"We'd already made our mind up that we were going to. Before we'd even got the information …] we just weren't getting sleep […] it's like, we have to do something"*	Communication as observed - Mismatches and misunderstandings	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Management of condition and practical implications)
Shilling_2011	*Doctor: "We've been using it for […] ten years or so […] and the whole idea of this study is to do it properly and to get the proof that it works so that we can use it more widely and for many more doctors to prescribe it, if it, if it is successful" [recorded recruitment consultation]* *"in order to get that tablet he has to participate in the trial" [interview with mother who declined the RCT]*	Communication as observed - Mismatches and misunderstandings	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Shilling_2011	*Doctor: "The hormone is given through err … an infusion. It's called err a syringe pump basically, which is, you know, puts medicine to the veins. Um and we will give it once a day" Mother: "OK"* *Doctor: All these procedures won't cause distress to your baby […] if your baby is not getting fully milk feeds, then we will use the lines. Once a baby is going on to full or milk feeds, then we will give drops and things […] so it won't cause any distress" [recorded recruitment consultation]*	Communication as observed - Mismatches and misunderstandings	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of treatment groups and unanswered questions

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Shilling_2011	*"I didn't see why I […] could say 'no' to it. Because I thought, well it's, you know, a 50/50 chance of her getting […] this additional help which she might need"*	What influences decision making: Benefits to the child, the family and others	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Hopes and fears)
Shilling_2011	*"Maybe he might get [the trial drug], maybe he mightn't. Maybe, if he does get it, it might help him in some way and if he doesn't get it then, you know, at least I tried to help [you] with the study"*	What influences decision making: Benefits to the child, the family and others	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Responsibility)
Shilling_2011	*"What my question is, if they say he's gonna take the placebo, […], the dummy one what is he going to benefit from the study?"*	Communication as observed - Parents interactivity in the trial discussion	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Understanding of treatment groups and unanswered questions)
Snowdon_1997	*"I suppose what they're saying is that er if at the end of the day conventional really really really isn't going to work for him then that [ECMO] would be absolutely ideal because... the chances are maybe he would be picked."*	What were parents' understanding of the basis of treatment decisions	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Understanding of treatment groups and unanswered questions)
Snowdon_1997	*"I thought that the doctor had entered Timothy for the trial as he was perfect for the ECMO treatment."*	What were parents' understanding of the basis of treatment decisions	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise)
Snowdon_1997	*"I just felt there could have been ten other babies with exactly the same problems as him and now there is nine sets of parents who are now being told that their baby's not being accepted onto the trial. And I did feel a bout of guilt for that but I could have gone out and...danced on water...when I got told that he'd been accepted." [Robert ECMO].*	What were parents' perceptions of why randomization was used: Clinical resources	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy (Vulnerability, Relief, Happiness)
Snowdon_1997	*"unfair" [Janet: Coventional Management and Gary: ECMO], "hard" [Mary: ECMO], "tough" [Alan: ECMO], and "heartless" [Angela: Coventional Management].*	Acceptance of Randomization	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and responsibility
Snowdon_1997	*"I feel desperately sorry for parents who, you know, were turned down particularly if their child doesn't live. I think it would be hard but I can see that it is necessary in case ...the research shows that ECMO is actually detrimental to children" [Mary: ECMO]*	Acceptance of Randomization	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - A difficult decision
Snowdon_1997	*"I suppose trials have to be a bit heartless, but you'd think that when the baby looks like they're dying, you'd think they'd just say... Oh hell you know... let's try the ECMO, see if it saves this baby... but with that sort of a trial they can't do that can they? They have to say, Well look, this baby looks like it's dying but I'm sorry it's getting conventional treatment and that's that." [Angela: Coventional Management].*	Acceptance of Randomization	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - A difficult decision
Snowdon_1997	*"lucky" [mentioned by a number of participants]*	Acceptance of Randomization	An emotional response to randomisation and expressions of preference for treatment: Fate and luck

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Snowdon_1997	*"it's not something that you would expect because when you go into a hospital you think right, it's a baby, they are going to do whatever is necessary for the baby, you know." [Fatima: Coventional Management].* *"anybody eligible for it should use it." [Fatima: Coventional Management].*	Rejection of Randomization	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise)
Snowdon_1997	*"I think any parent wants to try anything, you know, they don't sit down and think it's research, there could be side effects or there could be abnormalities that might come up. I think as parents...your first instinct is to save your baby." [Fatima: Coventional Management].*	Rejection of Randomization	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and responsibility
Snowdon_1997	*"they ought to have known which... [was] best" ... "He almost made it come across as it's the only thing we've got left to try and to me they ought to have tried it... [if it was] their opinion that he should have gone, then he should have gone, but if they thought, well he's better off staying here, then he should have stayed here" [Nick: Coventional Management].*	Rejection of Randomization	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise) (Anger)
Snowdon_1997	*"Yes, by randomization and that--that annoyed me. It didn't annoy me at the time because we got it (ECMO) but since then the very thing that's stuck in my mind all the time is who gives them the right to play God with babies" lives? And why the hell have we got it on trial when it's been in the States and it's got an 89% success rate or whatever...? Why is the National Health playing around with this? You know they wouldn't play around if America suddenly came up with a cure for cancer... Why are they playing around with babies' lives? Er, you know who gives them the right to sit there with say 10 babies and think well this--this one here you know will--will suit the trial, you know. Why not all 10 of them? Why isn't it available everywhere so everybody has a fair chance?" [Robert: ECMO].*	Rejection of Randomization	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise) (Anger)
Snowdon_1997	*"Even if she had been randomized out that bed would still have been available, wouldn't it? I couldn't come to terms with that at all. Now by all means fill the beds up and if babies come along that can't get into the beds then that is fine but this randomization of having a bed and a team and not being able to get into the bed was er--well I just couldn't come to terms with that which is why I would question.., the system of randomization." [Gary: ECMO].*	Rejection of Randomization	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise)

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Snowdon_1997	*"I knew it was random. I mean this is the whole thing about the Fate thing. I tell you it's kind of going through [your] whole life without following religion or anything like that but at that time you cling on to anything really and I thought there is only one decision here and it has to be Fate... I thought well if there is any justice in the world then the decision will come through right and as far as I'm concerned I mean that's what happened. He stayed and had traditional treatment and the fact that he didn't go to the ECMO as far as I'm concerned the decision was right. Fate played its hand" [Neil: Coventional Management]. "God's hand" [Andrea describing Robert's view: Coventional Management]. "justice" [Pascal: ECMO, and Neil: Coventional Management]. "very deep faith in God." [Mary: ECMO described her own and her husband's faith].*	Rejection of Randomization	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility / Fate and Luck
Snowdon_1997	*"It probably would have killed me if I had known that it was a randomized test and if they had turned around and said she couldn't go on, urn, you know...because I knew the ventilator wasn't helping her which meant...as good as "I am sorry there is nothing else we can do but wait for her to die." [Fatima: Coventional Management].*	Rejection of Randomization	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility
Snowdon_1997	*"We went back to the ward. The nurses said "Oh, he hasn't got the ECMO, he's staying here" and them saying that we thought, oh dear, you know, we've had the wrong one or something. We felt disappointed." [Paul: Coventional Management].*	Rejection of Randomization	An emotional response to randomisation and expressions of preference for treatment: Disappointment

Parents' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Woodgate_2010	*"I'm sure if he had been chosen for any other arm except for the difficult one, I would not have given it another great thought. But it all came down to the fact that he got chosen for the one with so much more intravenous and lumbar puncture medication, then it threw me for a loop and I went through a very touch period. Not the initial period because you have 56 days before you get randomized. So you have a long time before you get randomized. I would have been fine if they had put him on the easier arms of the study. But the minute that it hit me full in the face was when we got chosen for the tough arm that hit me like a lead brick." (randomised to active treatment)*	Coming to terms with my decision	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility
Woodgate_2010	*"She (the doctor) said had it been her child and this was chosen (standard treatment) for him probably she would do exactly as I am doing, and that was enough to make me calm I She too agreed with what I'm saying and feels that it's a wise decision. That was enough to make me at peace again. And now whatever happens with [child's] treatment, relapse or whatever, I will never look back and say I've made a poor decision. I will not do that." (randomised to active treatment)*	Coming to terms with my decision	An emotional response to randomisation and expressions of preference for treatment: Vulnerability and Responsibility
Woolfall_2013	*''I've got sort of a 50/50 chance of either she gets the drug or she gets the placebo. But she wouldn't be getting it otherwise.''*	Parents' agenda items: Access to medication	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Woolfall_2013	*"I'd heard about , [name of trial drug] and I'd read a few things on the internet, because of , [child's] sleeping, and I just thought, right I'm going to ask if he can have it."*	Parents' agenda items: Access to medication	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Woolfall_2013	*''if he does get the ,[name of trial drug] on this trial it will help him have a good night's sleep.''*	Parents' agenda items: Clinical benefit	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Management of condition and practical implications
Woolfall_2013	*''I was just thinking I hope he gets the, [Name of trial drug] one.''*	Parents' agenda items: Clinical benefit	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Woolfall_2013	*''We had to weigh it up against the fact that…. it could be a placebo anyway, it might not be the trial medication."*	Parents' agenda items: Randomisation	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Woolfall_2013	*"I wonder who does actually makes the decision, who goes on what and who doesn't"*	Misunderstandings linked to agenda items: Randomisation	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of trial processes (nature of RCT, randomisation, equipoise)
Woolfall_2013	*"We'd already made our mind up that we were going to. Before we'd even got the information […] we just weren't getting sleep […] it's like, we have to do something."*	Parents' misunderstandings Linked to Agenda Items: Access to medication	Parents' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Perceived benefits and risks / facilitators and barriers to trial participation
Woolfall_2013	*"It's called err a syringe pump basically, which is, you know, puts medicine to the veins." [recorded recruitment consultation]* *"[Doctor] told me, I think, they're going to put like kind of a small tube inside him…I just didn't like the idea from the beginning so I didn't give it more attention." [interview with mother who declined the RCT]*	Parents' misunderstandings Linked to Agenda Items: Practical implications of trial procedures	Parents' preferences for treatment: expressed while making sense and asking questions about the RCT - Understanding of treatment groups and unanswered questions (Vulnerability, responsibility and Fears)

Young peoples' data			
Author	**1st order constructs (original papers)**	**2nd order constructs (Theme names original papers)***	**Overarching 3rd order construct and sub-themes (translation/synthesis)**
Lock_2010	*"I was a bit disappointed actually because I just wanted to get rid of it [sore throat] straight away." [Participant, age 15].*	Management of recurrent sore throats: Requesting tonsillectomy	An emotional response to randomisation and expressions of preference for treatment: Disappointment
Shilling_2011	*"I was thinking, this could be really good for me but what if it's the placebo then, um, it's like I'm doing it for nothing basically." [Participant:11–14 years, interview].*	What influences decision making: young people - what is important to young people when considering a trial	Participants' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Shilling_2011	*"You just think like 'oh […] what are we gonna have to do' like, 'what medicines are we gonna take' and then obviously […] 'what will happen as a consequence of the medicine" (F57, 11–14 years)*		Participants' preferences for treatment: expressed while making sense and asking questions about the RCT: Understanding of treatment groups and unanswered questions
Shilling_2011	*"It would benefit me and other children in the future for like if they have the same thing they can get medicine and not have to do the study but like get it straight away because I helped" [Participant:11–14 years, interview].*		Participants' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Perceived benefits and risks (facilitators and barriers to trial participation)
Shilling_2011	*"They basically said that some people would get the real thing and others needed to get the placebo" [Participant:11–14 years, interview].*	Young people's experiences of the trial approach	Participants' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Access to treatment, medication or therapy
Shilling_2011	*'Even though one of them might not work for the bones and things will it do some good for me?' [Participant:11–14 years, recruitment consultation].*	Young people's interactivity in the trial discussion	Participants' preferences for treatment: expressed motivations and reservations about taking part in an RCT - Perceived benefits and risks (facilitators and barriers to trial participation)
**Findings and discussion points from original papers were analysed but are not included in this table.*			

Appendix 3: SMILE

[Reference: Crawley, E., et al., Comparing specialist medical care with specialist medical care plus the Lightning Process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial). Trials, 2013. ***14****: p. 444. http://www.ncbi.nlm.nih.gov/pubmed/24370208]]*

SMILE: Inclusion/exclusion criteria

Inclusion criteria
Children will be included if they have been diagnosed with CFS/ME (made using NICE guidance*) and are between 12 and 18 years old inclusive. *[*NICE: National Institute for Health and Clinical Excellence, Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) Diagnosis and management of CFS/ME in adults and children., N.I.f.H.a.C. Excellence., Editor. 2007, Developed by the National Collaborating Centre for Primary Care: London].*
Exclusion criteria
Children will be excluded if: they are too severely affected to attend hospital appointments (defined as children and young people that do not regularly leave their house), or if they or their parents have insufficient English to either understand the Patient Information Leaflet (PIL) and consent form to take part in the Lightning Process or take part in the interviews.

SMILE: Eligibility assessment

Eligible young people were identified by health professionals at their initial clinical appointment with the specialist CFS/ME team. The initial clinical appointment included: an assessment of symptoms, diagnosis, treatment plan and an introduction to the SMILE trial, it lasted approximately 90 minutes. The specialist multi-disciplinary team included paediatricians, occupational therapists, physiotherapists and clinical psychologists providing a satellite service from several hospitals and health centres in the South-West of the UK.

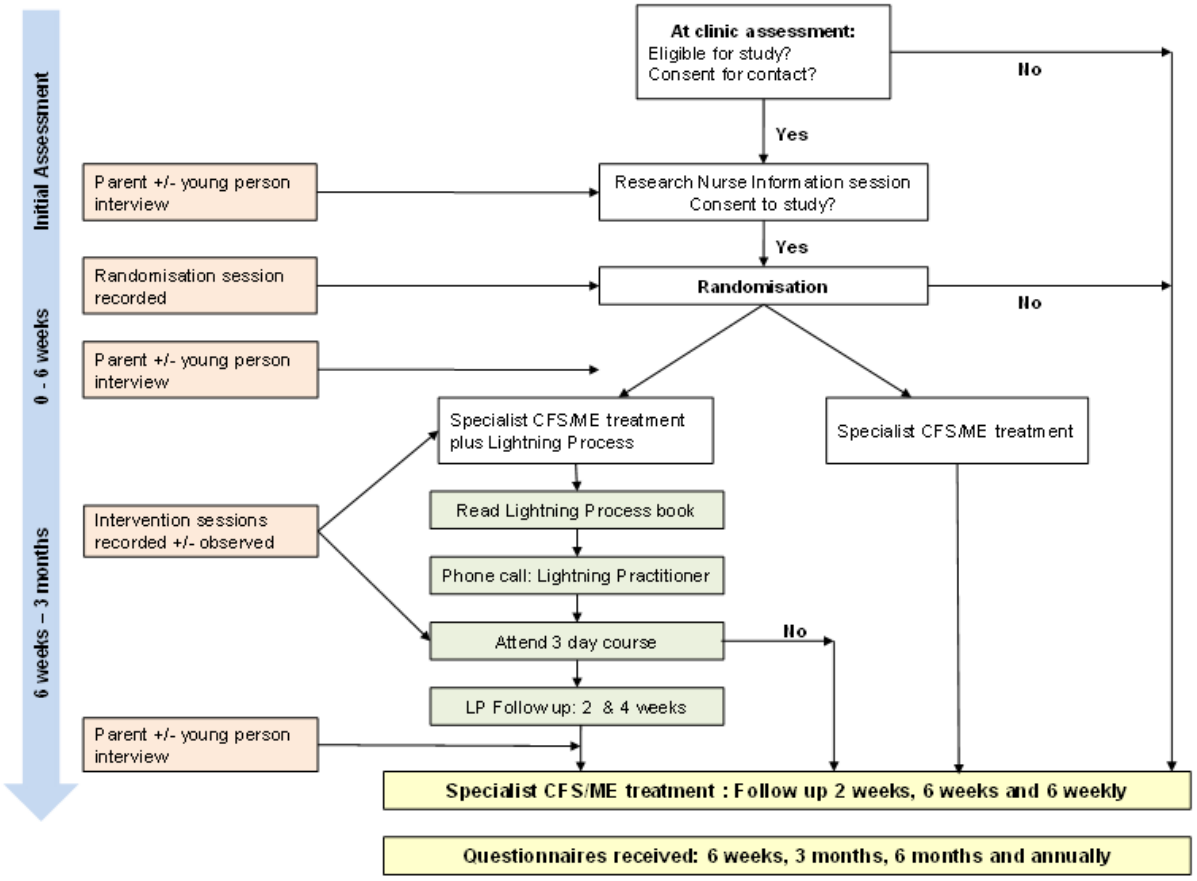
Young patients were initially assessed for CFS/ME symptoms, and those that were given a diagnosis of CFS/ME and were eligible for the trial were informed about potential participation in a feasibility RCT at the end of their clinical appointment. These families were given a brief verbal overview of the RCT, and the relevant patient and parent information leaflets were given to families who were interested in finding out more about the trial. The health professional also asked families if they were willing to be contacted by a researcher (LB) and a recruiter working on the SMILE research team. Consent to contact was obtained from families who were willing to hear more about the trial. If families were willing to provide reasons for declining contact from the research team these were recorded and passed on anonymously to the research team.

SMILE: Integrated qualitative aims and objectives

1. To assess the recruitment process, including views and experiences of the initial assessment/eligibility appointment, recruitment to trial appointment, provision and acceptability of patient information, and reasons for accepting or declining participation in the trial.
2. To explore prior exposure, beliefs, expectations and preferences about specialist medical care and Lightning Process interventions before assignment, post-randomisation, and experiences and acceptability of the intervention and outcome after having received it.
3. To investigate appropriate patient-reported outcome measures for the RCT, including views and experiences of completing the Hospital Anxiety and Depression Scale (HADS), the Profile of Mood States (POMS), and the Spence Children's Anxiety Scale (SCAS).
4. To observe the delivery of both interventions to provide data on setting, implementation and acceptability.

SMILE: Trial flow

Participant flow through trial related interventions and data collection procedures.



[Reference: Crawley et al 2012, Comparing specialist medical care with specialist medical care plus the Lightning Process for Chronic Fatigue Syndrome or Myalgic Encephalopathy (CFS/ME) Randomised Controlled Trial. SMILE – Specialist Medical Intervention & Lightning Evaluation]

SMILE: Data collection and randomisation

Allocation (ratio 1:1) was concealed and minimised by age (categories 12-15 or 16-18 years) and gender. A telephone-based interactive voice response system was used to randomise participants. This was maintained by the Bristol Randomised Trials Collaboration. Because of the nature of the interventions, it was not practical to blind either the family or the clinical service to treatment allocation.

After allocation the recruiter informed the clinical service of the patient's allocation, (by phone or email) to enable the clinical team to send a letter with details of the patient's next follow-up appointment. When relevant, the recruiter also informed the Lightning Process group (via telephone) so that a Lightning Process introductory book could be sent out to the participant, and a Lightning Process practitioner could make contact with the family. The participant's GPs was informed via letter, that their patient was participating in the SMILE trial, and which intervention the young person had been allocated.

Recording of first clinical appointment

A sample of initial assessment appointments were audio-recorded by the research team to document the interaction between health care professionals and potentially eligible families, specifically the way in which the SMILE trial was introduced to families. All Lightning Process courses were audio-recorded and a researcher (LB) observed the delivery of 25% of the LP courses. Data from Lightning Process courses was not used in the current thesis but some data from initial clinical appointments was used during the qualitative data analyses to provide contextual information in relation to the consent to contact process.

SMILE: Intervention groups

Specialist medical care leaflets for paediatric CFS/ME patients

The link below provides current versions of the CFS/ME specialist medical care program leaflets. These have been updated since the SMILE RCT but the fundamental principles remain the same:

http://www.ruh.nhs.uk/patients/services/clinical_depts/paediatric_cfs_me/leaflets.asp?menu_id=1

- Activity, rest, and sleep diary
- CBT leaflet
- Energy management
- Exam Stress
- Exercise Chart
- Information for Schools and Colleges
- Managing feelings
- Sleep & Relaxation

Skype appointments were not available at the time of the SMILE RCT

Lightning Process

In the community Lightning Process courses would be available to participants of any age with a range of conditions (including: CFS/ME, fibromyalgia, depression, anxiety and obsessive-compulsive disorder). The Lightning Process course is a mixture of theory and practical sessions involving both group and individual discussions with those participating (3-5 participants per group during the SMILE RCT). In the theory sessions, SMILE participants learned about stress and its physical effects, how the mind and body interact and how thought processes can be helpful and unhelpful. In the practical sessions, they identified goals they wished to achieve (e.g. walking for longer) and were given different ways to think about and prepare for this. They then had the chance to practise this on the course with the Lightning Process practitioner there to support them. Participants were given up to 30 minutes of homework each day so they could continue to practise the skills they had learnt, using a goal they identified during that day's session. The Lightning Process was not a treatment offered by the specialist paediatric CFS/ME service outside the trial, but if parents wished they could access this treatment by paying for the course which cost approximately £620 if accessed privately (course cost when the SMILE protocol was published 2013). The Lightning Process course was (and is currently) not offered or paid for by the NHS outside of the SMILE trial. During the SMILE trial it was made clear to families that they were free to access this course outside the NHS if they wished and were able to do so.

SMILE: Patient Information Leaflet (12-18yrs)

v9 May 2011

CFS/NHS/PAEDIATRICS - Specialist help for ME.

SMILE
Specialist Medical Intervention & Lightning Evaluation

Feasibility randomised controlled trial for Chronic Fatigue Syndrome/ME

INFORMATION LEAFLET FOR TEENAGERS

We would like to invite you to take part in a research study which will tell us whether it is possible to study specialist medical care compared to specialist medical care plus the Lightning Process as interventions (ways to help) for Chronic Fatigue Syndrome or Myalgic encephalopathy (CFS/ME) in teenagers.
Before you decide to take part it is important for you to understand *why* the study is being done and *what* it will involve. Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us if you want to. We would like to go through this information with you and we think this will take about 20 to 30 minutes. The leaflet is divided in to two parts. Part 1 tells you about the study and what will happen to you if you take part. Part 2 gives details about how the study will be run.
Ask us if there is anything you don't understand or if you want more information. Take time to decide whether or not you want to join in.

Thank you for reading this!

Part 1

Why are we doing this study?

1. We want to find out whether it is possible to do a study investigating specialist medical care with or without the Lightning Process. To do this, we need to know whether young people will take part.
2. We also want to find out more about the differences between the Lightning Process and specialist medical care. We are particularly interested in your views of both interventions.
3. As part of this study, we will also try and study the cost of the illness to families and measure the cost of treatment.
4. We know that the questionnaires we are using don't always suit teenagers with CFS/ME so we are going to use this study to understand more about what you think about the questionnaires we use.

What is Specialist Medical Care?

Specialist Medical Care is the current treatment teenagers normally receive if they have CFS/ME. They normally have a follow up phone call at 2 weeks followed by individual family based sessions with a member of the Bath Specialist CFS/ME team. This could be a physiotherapist, psychologist or occupational therapist depending on your goals and where you would like to receive follow up. You will be offered either activity management, Cognitive Behavioural Therapy (CBT), graded exercise or a mixture of all three depending on your goals and needs. The timing and number of the sessions depends on your needs but on

average, most teenagers have three or four follow up sessions, spread out over 3 to 6 months usually at 6 weeks and then every 6 weeks.

What is the Lightning Process?

The Lightning Process is based on the idea that the body and mind work together to affect your health. It is a training programme, run as a course on three consecutive days (for 3 hours 45 minutes a day) in a group with up to five other young people aged between 12 and 18 years old. The course is run by a Lightning Process Practitioner. Lightning Process Practitioners are trained in Neuro Linguistic Programming (NLP), life coaching, clinical hypnotherapy and the Lightning Process – they are not medically trained. The courses will be held somewhere near you, either in a clinic or hospital, or in a hotel or community hall. Where ever it is held, it will be suitable for the course and for young people your age.

There are regular breaks throughout the course and a mixture of group and individual discussions. Each day the course will include a theory session and a practical session. In the theory session, teenagers learn about stress and its physical effects, how the mind-body interacts and how thought processes can be helpful and unhelpful. In the practical session, teenagers identify goals they wish to achieve (for example, standing for longer) and are given different ways to think about and prepare for this. They then have the chance to practise this on the course with the Lightning Process practitioner there to support them.

A parent can attend and a researcher may be present to watch the session. Teenagers are given up to 30 minutes homework each day so they can continue to practise the skills they have learnt using a goal they identified on the course.

Why have I been asked to take part?

You have been asked if you want to take part because you are between 12 and 18 years of age, have CFS/ME and have attended an assessment at the Bath Specialist CFS/ME service.

We do not think you should take part if you are severely affected (cannot leave the house) or if you do not speak English. You should not take part if there is one intervention you don't want to do for example, if you aren't comfortable working in groups.

Do I have to take part?

You do not have to take part in this study. If you agree to meet the researcher who will ask you about your views about the interventions or the nurse who will explain more about the study, this will not commit you to taking part in the study.

If you decide to take part but change your mind later, we will continue to follow you up like we do other teenagers who are not part of the study unless you tell us you don't want us to You can withdraw from the study at any point and if you want us to we will take out the information collected at interview at any point before we carry out data analysis

We hope that up to 90 young people and their parents will take part in this study but it is up to you to decide whether or not to take part. If you decide not to take part or decide to withdraw at any time, this will not affect the standard of specialist medical care you would normally receive.

What are we asking you to do?

First stage:

If you agree to take part in this study, a researcher may arrange a time to interview you in the next two weeks at a place and time that is convenient for you and your family to find out what you know about the Lightning Process and what your views are about the different types of intervention. The interview will be audio-recorded with your permission and will last for around 20 minutes.

If you (and your parent if you are under 16) agree to proceed, a research nurse will then arrange to visit you at home (or a location of your choice), spend some time with you to discuss the two different interventions and explain more about the study. If you are willing to take part, you will be randomly allocated (in other words, by chance) to one of two intervention groups: either specialist medical care or specialist medical care plus the Lightning Process. As this study is trying to find out whether we can compare both groups, it will not be possible for you to choose the group. The group that you will be part of will be determined by computer at random. This is the same as rolling a dice.

Second stage: In the second stage you will be part of group 1 which is Specialist Medical Care) or group 2 which is Specialist Medical Care plus the Lightning Process.

Group 1: Specialist Medical Care

If you are in group 1, you will receive specialist medical care.

Group 2: Specialist Medical Care plus the Lightning Process

If you are in group 2, you will receive specialist medical care and the Lightning Process. In addition to the specialist medical care described above, you will be asked to read the “Introduction to the Lightning Process” book (140 pages) or listen to the audio book before you attend the lightning process course. Your parents/guardian will be asked to read or listen to the Lightning Process book as well. You will then need to complete an assessment form asking about what goals you have set and what you have learnt from reading the book/listening to the audio book.

After this, the Lightning Process Practitioner will phone and talk to you and your parents/guardian to check that having found out more about what is going to happen you are still happy with attending the course. They will discuss your goals and the content of the book you have read with you and your parent/guardian. This is an opportunity for you to ask questions and find out more about the Lightning Process.

If you or your parents need more time to talk to the Lightning Process Practitioner, you can arrange other phone calls with them.

If you are happy to attend the course, you will be booked on to the Lightning Process course which will run on three consecutive days (for 3 hours 45 minutes a day). You will be in a group with up to five other young people aged between 12 and 18 years old who are also involved in the study. After the Lightning Process course, you will be offered two follow up phone calls at 2 and 4 weeks at a time that is convenient for you. This will be in addition to the specialist medical follow up sessions as above. You can cancel follow up sessions at any stage if you feel you do not need or want them.

Group 1 and Group 2

After you know which intervention group you are in, we may interview you (if you haven't already been interviewed) to find out what you felt about the process of randomisation or we may interview you after the intervention to find out what you feel about it and how you found completing study questionnaires. We will only interview you once. Interviews will take approximately 20 minutes and will be held at your home or a location of you and your parents/guardians choice.

We want to find out more about both interventions. The intervention sessions will be audio-recorded and for about half the interventions, the researcher will also observe the session.

Whether you take part in this study or not, you will receive questionnaires by post at 6 months and a year to check how you are doing. Each pack of questionnaires takes about ten minutes to complete. If you take part in this study, you will receive two more questionnaires at each time point, than teenagers who do not take part in the study. These questionnaires are to help us understand more about which questionnaires we should use and to find out more about the cost of treatment and the cost of the illness. They will take you an extra five minutes (or so) to complete. We will also send questionnaires to you at 3 months after the intervention.

We will ask your school with your permission about how much you have been at school when we first see you and at follow up.

Do I have to take part?

You do not have to take part in this study. If you agree to meet the researcher who will ask you about your views about the interventions, or the nurse, who will explain more about the study, this will not commit you to taking part in the study.

We hope that up to 90 young people and their parents will take part in this study but it is up to you to decide whether or not to take part. If you decide not to take part or decide to withdraw at any time, this will not affect the standard of specialist medical care you would normally receive.

Are there any disadvantages of taking part in this study?

You may need to spend time talking to a researcher for about 20 minutes so we can understand what you think about the study and the sessions either before or after you have them. You will need to spend 20 minutes talking to the research nurse about the study. If you take part, you will need to complete questionnaires at 3 months after the interventions as well as the normal time points (6 months and annually). You will also need to complete 2 more questionnaires at each time point that we think will take about 5 minutes to complete. You may not find the intervention arm you have been offered helps you. This could be true for both interventions. Teenagers with CFS/ME can get worse with any intervention offered. There is no data in teenagers, see tables 1 and 2 for data in adults. Some parents of children who receive Specialist Medical Care and the Lightning Process have told us that they find the two approaches and the language used is different. If this is a problem for you, we will talk about it with you and offer support.

Are there any side effects of the interventions?

We do not think there are any side effects of the interventions but because the Lightning Process has not been tested before, we will be monitoring all interventions and closely following up all young people who take part.

Benefits of joining in

There are no specific benefits for you in taking part in this study. If we understand more about the interventions, taking part in this study may help other teenagers with CFS/ME in the future.

What happens when the research study stops?

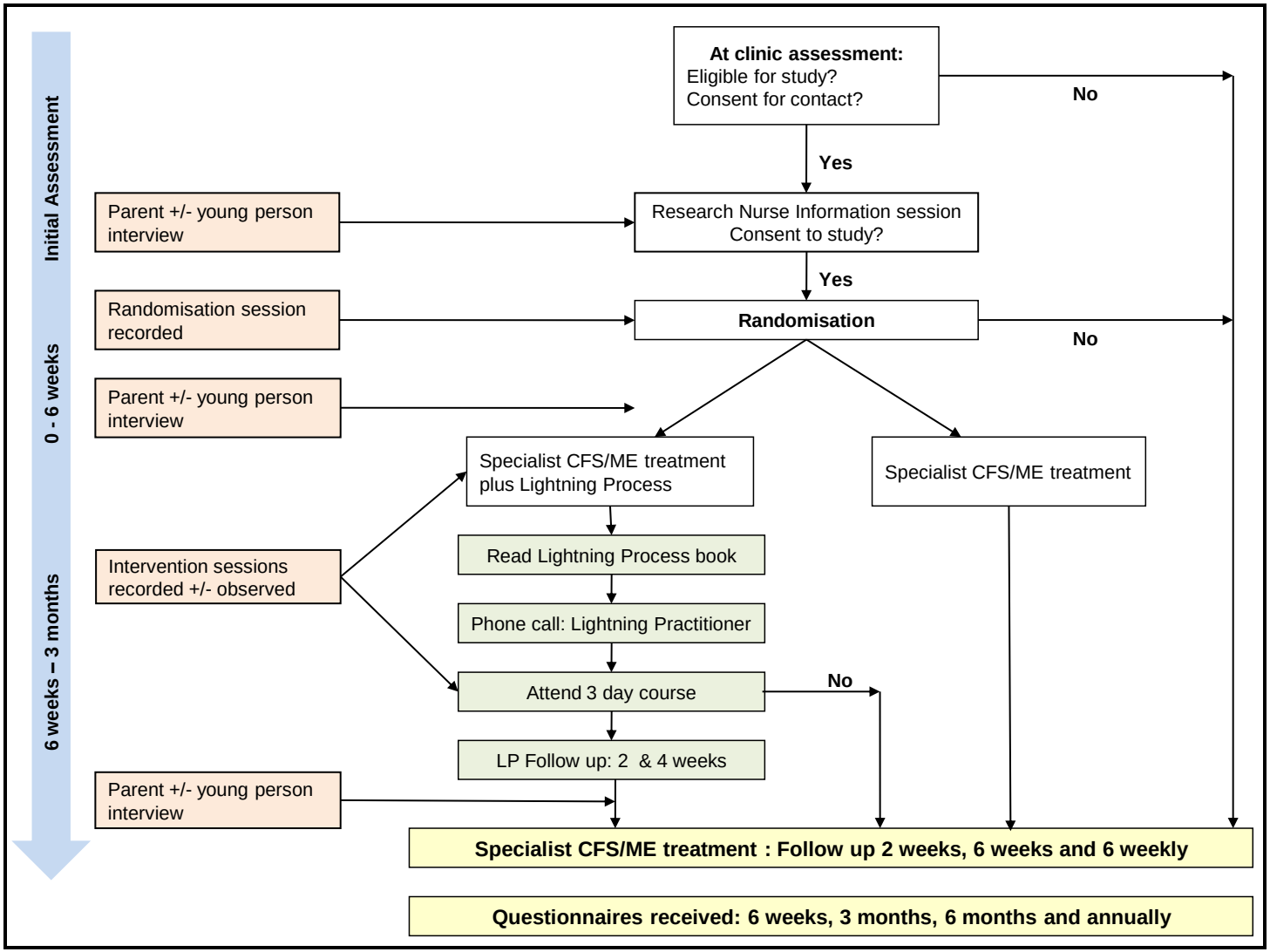
After the study stops, you will continue to access specialist medical care if you still need it. You will also continue to receive follow up questionnaires, like the teenagers who did not take part in the study.

What if there is a problem?

We will try and deal with any problem you have during this study. Detailed information is given in part 2.

Will my details be kept private?

Yes. Your privacy is important to us and all your details will be handled in confidence. The details are included in part 2.



SMILE: Protocol Flow Chart

If the information in Part 1 has interested you and you are considering taking part in this study, please read the additional information in Part 2 before making any decision.

What if new information becomes available?

Sometimes during the course of a research study, new information becomes available about the interventions that are being studied. If this happens, we will tell you about it and discuss with you whether you want to continue in the study.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point and this will not affect the care that we give you. We will keep the information that we have collected up to the time you leave the study but this is completely private and nobody will know it is you. You will continue to receive the follow up questionnaires that other teenagers receive who are not part of the study but you can tell us if you do not want these and we will stop sending them to you.

What should I do if I have a problem with this study?

If you have any problems with this study, please speak to PI DETAILS or any member of the clinical team that you know. You would be able to complain to the NHS in the usual way if you were not happy with the study through the Patient Advice and Liaison services (PALS) 01225 473424.

In the event that something does go wrong and you are harmed during the research and this is due to someone being careless then you may be able to take legal action to get repayment from the hospital but your parents may need to pay a lawyer to help you. You can also use the normal National Health Service system for complaints if you want to.

Does everybody involved in the study have the appropriate police checks?

Yes. All those working in the study have had the necessary police checks to make sure they are safe to work with children and young people.

Your privacy

It is very important that all the information you give us is completely private. We will write down the things that you say from the audio-recording and take out any details linking the recording to you so that nobody will know that it was you. We may use small bits of what you say when we report the study, but the quotes will be completely anonymised so nobody will know it was you. The recording will be encrypted and password protected (so no-one else can listen to it) before it is stored on a secure university server. The copy of what you said in the interview (the transcript) will be linked to you and your parents via a code. All personal details or lists that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS computers.

All questionnaires that you fill out are anonymised before they are given to you. We will give you a 13-digit identification code that will be on the top of the questionnaires. A list of names and corresponding identification numbers are kept separately and securely on a password protected NHS server.

If you tell us something that makes us worried about your safety, we may have to discuss this with somebody else as we need to be sure you are safe. This means, what you say would not be kept completely private. We would do the same if you told us something in clinic.

Data protection

All data is completely anonymised and is kept on secure encrypted password protected University Servers.

Consent

We have to be absolutely certain that you are happy to join in this study, so if you say you are, we will ask you to sign our consent form. We will also ask you to sign a consent form if we interview you. Even if you do sign the forms, you will be free to withdraw at any point. Just tell us if this is the case. Whether or not you wish to participate, you will continue to receive the same care from the clinical team.

Who will know I am taking part in the study?

We think your GP should know that you are taking part in this study because they need to know what happens to you and we will ask your permission to let your GP know.

What will happen to the results of the study?

This study will give us information about how much young people with CFS/ME use health services and will tell us more about which questionnaires we think we should use. We aim to publish these results in journals to help other people seeing teenagers with CFS/ME. If young people take part in this study, we will use the results to plan for a larger study to look at whether the Lightning Process is helpful or not.

Who is organising and funding the study?

This research is organised by Dr Esther Crawley who is the Clinical Lead for the Bath specialist CFS/ME service at the RNHRD and leads the Paediatric CFS/ME Research team at the University of Bristol. Dr Crawley is working with a group of researchers at the University of Bristol who are helping her with this study. The study is funded by The Linbury Trust and The Ashden Trust.

Will I need to pay to be part of this study?

No

Ethical Approval

The study has been approved by the South West 2 Research Ethics Committee. It has also been checked and approved by the RNHRD research committee.

Table 1. Data taken from Action for ME (AfME) and Association of Young people with ME (AYME) joint report "M.E. 2008: What progress". 2763 people answered this survey (7% were children and young people)

Intervention	Helpful (%)	No change (%)	Made worse (%)
GET	45	21	34
CBT	50	38	12
Lightning Process	53	31	16

*GET = Graded Exercise Therapy. CBT = Cognitive Behavioural Therapy.

For the full report:

http://www.actionforme.org.uk/Documents/get-informed/Survey%20Summary%20Report%202008.pdf

Also reported in Parliamentary enquiry found here:

http://www.actionforme.org.uk/Documents/get-informed/APPG%20Report%20FINAL.pdf

Table 2. Data taken from 2008 MEA survey of 4217 people (<5% where children and young people)

Answer Options	Response count	Greatly improved	Improved	No change	Slightly Worse	Much worse
GET	906	3.4	18.7	21.4	23.4	33.1
CBT	997	2.8	23.1	54.6	11.6	7.9
LP	101	25.7	18.8	34.7	7.9	12.9

*GET = Graded Exercise Therapy. CBT = Cognitive Behavioural Therapy. LP = Lightning Process

For the full report:

http://www.meassociation.org.uk/wp-content/uploads/2010/09/2010-survey-report-lo-res10.pdf

Also reported in Parliamentary enquiry found here:

http://www.actionforme.org.uk/Documents/get-informed/APPG%20Report%20FINAL.pdf

Contact / Further Information:

XXX Or if you want to talk to somebody independent please contact XXX

THANK YOU for taking the time to read this leaflet

SMILE: Parent Information Leaflet

v9 December 2010

CFS/NHS/PAEDIATRICS - Specialist help for ME.

SMILE
Specialist Medical Intervention & Lightning Evaluation

Feasibility randomised controlled trial for Chronic Fatigue Syndrome/ME

INFORMATION LEAFLET FOR PARENTS

We would like to invite you to take part in a research study which will tell us whether it is possible to study specialist medical care compared to specialist medical care plus the Lightning Process as interventions for Chronic Fatigue Syndrome or Myalgic encephalopathy (CFS/ME) in children.

Before you decide to take part it is important for you to understand *why* the study is being done and *what* it will involve. Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us if you want to. We would like to go through this information with you and we think this will take about 20 to 30 minutes. The leaflet is divided in to two parts. Part 1 tells you about the study and what will happen to you and your child if you take part. Part 2 give details about the conduct of the study.

Ask us if there is anything you don't understand or if you want more information. Take time to decide whether or not you want to join in.

Thank you for reading this!

Part 1

Why are we doing this study?

1. We want to find out whether young people will take part in a study comparing specialist medical care with or without the Lightning Process.
2. We also want to find out about the differences between the Lightning Process and specialist medical care and your views them.
3. We will study the cost of the illness to families and measure the cost of treatment.
4. We know that the questionnaires we are using don't always suit children and young people with CFS/ME so we are going to use this study to understand more about what your child thinks about the questionnaires we use.

What is Specialist Medical Care?

Specialist Medical Care is the current treatment children normally receive if they have CFS/ME. After their assessment, they will have a follow up phone call at 2 weeks followed by individual sessions with a member of the Bath Specialist CFS/ME team. This could be a physiotherapist, psychologist or occupational therapist depending on your child's goals and where you would like to receive follow up. They will be offered either activity management, cognitive behavioural therapy (CBT), graded exercise or a mixture of all three depending on the goals and needs of your child. The timing and number of the sessions depends on your child's needs but on average, most young people have three or four follow up sessions, spread out over 3 to 6 months, usually at 6 weeks and then every 6 weeks.

What is the Lightning Process?

The Lightning Process is based on the idea that the body and mind work together to affect your health. It is a training programme, run as a course on three consecutive days (for 3 hours 45 minutes a day) in a group with up to five other young people aged between 12 and 18 years old. The course is run by a Lightning Process Practitioner. Lightning Process Practitioners are trained in Neuro Linguistic Programming (NLP), life coaching, clinical hypnotherapy and the Lightning Process – they are not medically trained. The courses will be held somewhere near you, either in a clinic or hospital, or in a hotel or community hall. There are regular breaks throughout the course and a mixture of group and individual discussions. The daily seminars will include a theory session and a practical session. In the theory session, children learn about stress, how the mind-body interacts and how thought processes can be helpful and unhelpful. In the practical session children and young people identify goals they wish to achieve (for example, standing for longer) and are given alternative ways to think about and prepare for this. They then have the opportunity to practise this on the course with the Lightning Process practitioner there to support them.

A parent can attend and a researcher may be present to observe the session. Young people are given up to 30 minutes homework each day so they can continue to practise the skills they have learnt using a goal identified by the young person on the course.

Why has my child been asked to take part?

You child has been asked if they want to take part because they are between 12 and 18 years of age, have CFS/ME and have attended an assessment at the Bath Specialist CFS/ME service.

We do not think your child should take part if they are severely affected (cannot leave the house) or if they do not speak English. Your child should not take part if there is one intervention they do not want to do, for example, if they don't feel comfortable working in groups.

Does my child have to take part?

Your child does not have to take part in this study. If you agree to meet the researcher who will ask you about your views about the interventions or the nurse who will explain more about the study, this will not commit you to taking part in the study.

If you decide to take part but withdraw later, we will continue to follow up your child as if they were not in the study unless you tell us you don't want us to. Your child can withdraw at any point in the study. Your child can withdraw their information collected at interview at any point in the study before analysis

We hope that up to 90 young people and their parents will take part in this study but it is up to you and your child to decide whether or not to take part. If you decide not to take part or decide to withdraw at any time, this will not affect the standard of specialist medical care you would normally receive.

What are we asking you to do.

First stage:

If you agree to take part in this study, a researcher may arrange a time to interview you in the next two weeks and during the study (on no more than three occasions) at a place and time that is convenient for you. This is to find out what you know about the Lightning Process and about your experience of each type of intervention. The interviews will be audio-recorded with your permission and will last between 20 minutes to an hour. Your child will be interviewed at one of these time points for approximately 20 minutes.

If you and your child agree to proceed, a research nurse will arrange to visit you at a location of your choice, to discuss the two different intervention options and explain more about the study. If you are willing to take part, your child will be randomly allocated to one of two intervention groups: either specialist medical care or specialist medical care plus the Lightning Process. As this study is trying to find out whether we can compare both groups, it will not be possible for you to choose the group for your child. The group that your child will be part of will be determined by computer at random (in other words, by chance).

Second stage:

In the second stage you child will be part of group 1 which is Specialist Medical Care) or group 2 which is Specialist Medical Care plus the Lightning Process

Group 1: Specialist Medical Care

If your child is in group 1, they will receive specialist medical care. While your child is in this intervention arm, we will ask them not to access the Lightning Process outside the study.

Group 2: Specialist Medical Care plus the Lightning Process

If you child is in group 2, they will receive specialist medical care and the Lightning Process intervention. In addition to the specialist medical care described above, young people in this group will be asked to read the “Introduction to the Lightning Process” book (140 pages) or listen to the audio book before they attend the lightning process course. You will be asked to read or listen to the Lightning Process book as well. Your child will then complete an assessment form asking about what goals they have set themselves and what they learnt from reading the book/listening to the audio book.

After this, the Lightning Process Practitioner will phone and talk to you and your child to check that having found out more about what is going to happen they are still happy with attending the course. They will discuss your child’s goals with both of you and the content of the book you have read. This is an opportunity for you or your child to ask questions, and find out more about the Lightning Process. You and your child may feel you need more time to discuss the Lightning Process with the Lightning Process Practitioner and you can arrange more telephone calls if you want to.

If you and your child are happy to attend a Lightning Process course, your child will be booked on to the Lightning Process course which will run on three consecutive days (for 3 hours 45 minutes a day) in a group with up to five other young people aged between 12 and 18 years old who are also involved in the study. After the Lightning Process course, you will have two follow up phone calls at 2 and 4 weeks at a time that is convenient for you. This will be in addition to the specialist medical follow up sessions as above. You and your child can cancel follow up sessions at any stage, if you feel you do not need or want them.

Group 1 and Group 2

The intervention sessions will be audio-recorded and for approximately half the interventions, the researcher will also observe the session.

Children in both groups (and those who do not take part) will receive questionnaires by post at 6 weeks, 6 months and a year to check how they are doing. Each pack of questionnaires takes about ten minutes to complete. If your child takes part in this study, they will receive two more questionnaires at each time point than children who do not take part in the study, which will take an extra five minutes (or so) to complete. These questionnaires are to help us understand more about which questionnaires we should use and to find out more about the cost of treatment and the cost of the illness. If you child takes part in this study, they will also receive questionnaires at 3 months (in addition to 6 weeks, 6 months and annually).

We will also contact your child's school at assessment and at each of these follow up time points to find out how much school they are attending.

If your child takes part in the study, we will also ask you to fill in three questionnaires at the start and two at follow-up, so we can understand more about the cost of this illness to your family and the cost of treatment. We estimate that these questionnaires will take you less than 10 minutes to complete.

Are there any disadvantages of taking part in this study?

You may need to spend time talking to us on three different occasions. We think this will take about 20 minutes each time but may take longer (no more than an hour). You will need to spend 20 minutes talking to the research nurse about the study. Your child may be interviewed as well but only at one time point and for no more than 20 minutes. If your child takes part, they will need to complete questionnaires at 3 months after the interventions as well as the normal time points (6 weeks, 6 months and annually). They will also need to complete two more questionnaires at each time point that we think will take about 5 minutes (or so) to complete.

You will need to complete three more questionnaires at the start and two questionnaires at follow up. This will take 10 to 20 minutes each time.

Your child may not find the intervention arm they have been offered helps them. This could be true for both interventions. Teenagers with CFS/ME can get worse with any intervention offered. There is no data in teenagers, see tables 1 and 2 for data in adults.

re there any side effects of the interventions?

We do not think there are any side effects of the interventions but because the Lightning Process has not been evaluated before, we will be monitoring all interventions and closely following up all young people who take part.

Benefits of joining in

There are no specific benefits for you or your child taking part in this study although some parents may find it helpful to talk to others about their experiences. If we understand more about the interventions, taking part in this study may help other children and young people with CFS/ME in the future.

What happens when the research study stops?

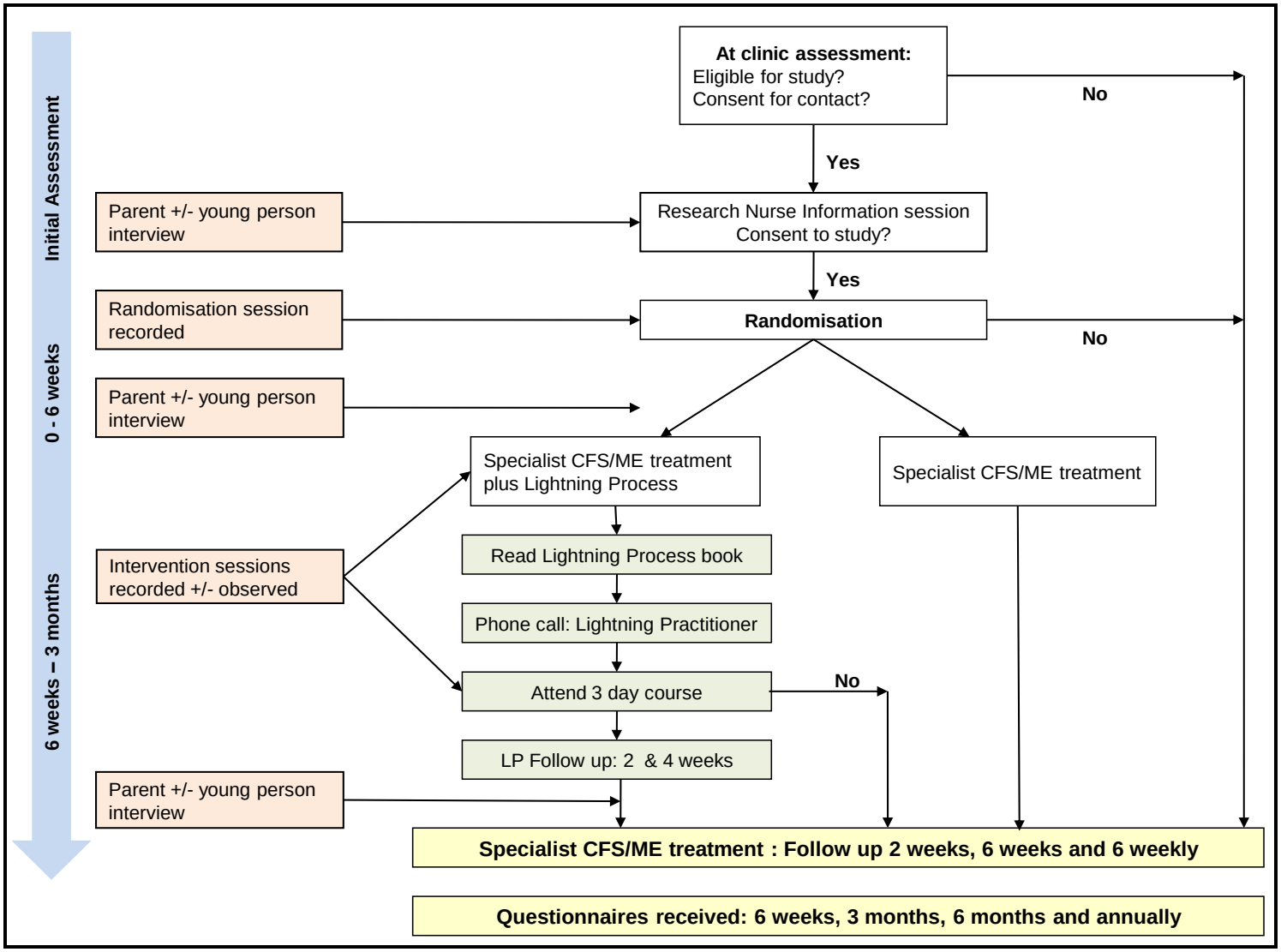
After the study stops, your child will continue to access specialist medical care if they still need it. They will also continue to receive follow up questionnaires like the young people who did not take part in the study.

What if there is a problem?

We will try and deal with any problem you or your child has during this study. Detailed information is given in part 2.

Will my details be kept private?

Yes. Your privacy is important to us and all your details will be handled in confidence. The details are included in part 2.



SMILE: Protocol Flow Chart

If the information in Part 1 has interested you and you are considering taking part in this study, please read the additional information in Part 2 before making any decision.

What if new information becomes available?

If new information becomes available, we will tell you about it and discuss whether you and your child want to continue in the study. If the study stops for any reason, we will tell you and your child and arrange continuing care for your child.

What will happen if I don't want to carry on with the study?

Your child can withdraw from the study at any point and this will not affect the care that we give them. We will keep the information that we have collected up to the point of withdrawal but this is completely anonymous and nobody will know it is your child. Your child will continue to receive the follow up questionnaires that other young people receive who are not part of the study but you can tell us if you do not want to complete this as well and we will stop sending them to your child.

What should I do if I have a problem with this study?

If you have any problems with this study, please speak to Dr Esther Crawley **(01225 465941. esther.crawley@bristol.ac.uk)** or any member of the clinical team that you know. You would be able to complain to the NHS in the usual way if you were not happy with the study by contacting the Patient Advice and Liaison services (PALS) 01225 473424.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation against the RNHRD, but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you (if appropriate).

Does everybody involved in the study have the appropriate police checks?

Yes

Your privacy

It is very important that all the information you and your child give us is completely private. We will write down the things that you and your child say from the audio-recording and take out any details linking the recording to you or your child so that nobody will know that it was you. We may use small bits of what you say when we report the study, but your quotes will be anonymised and nobody will know it was you. The recording will be encrypted and password protected (so nobody else can listen to it) before it is stored on a secure university server. The copy of what you said in the interview (the transcript) will be linked to you and your child via a code. All personal details or lists that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS computers.

All questionnaires that you fill out are anonymised before they are given to you. We will give you a 13 digit identification code that will be on the top of the questionnaires. A list of names and corresponding identification numbers are kept separately and securely on a password protected NHS server.

As with any child being seen in clinic, if we have concerns over your child's welfare, we may have to break confidentiality. In some cases, we may have to discuss your child with another professional such as a social worker or child protection officer.

Data protection

All data is completely anonymised and is kept on secure encrypted password protected University Servers.

Consent

We have to be absolutely certain that you are happy to join in this study, so if you say you are, we will ask you and your child to sign our consent form. We will also ask you to sign a consent form if we interview you, to check you are still happy. Even if you do sign the consent forms, you and your child will be free to withdraw at any point. Just tell us if this is the case. Whether or not you wish to participate, your child will continue to receive the same care from the clinical team.

Who will know I am taking part in the study?

We think your GP should know about the interventions your child receives and we will ask your permission to let your GP know.

What will happen to the results of the study?

This study will give us information about how much families use health services and will tell us more about which questionnaires we should use. We aim to publish these results in journals to help other health professionals. If it is possible to recruit young people into this study, we will use the results to plan for a larger study to look at whether the Lightning Process is helpful or not.

Who is organising and funding the study?

This research is organised by Dr Esther Crawley who is the Clinical Lead for the Bath specialist CFS/ME service at the RNHRD and leads the Paediatric CFS/ME Research team at the University of Bristol. Dr Crawley is working with a group of researchers at the University of Bristol who are helping her with this study. The study is funded by the Linbury Trust and The Ashden Trust.

Will I need to pay to be part of this study?

No

Ethical Approval

The study has been approved by the South West 2 Research Ethics Committee. It has also been checked and approved by the RNHRD research committee.

The details below were added to v9 of the young person and parent PIL due to trial controversy: The recruiter discussed families' feelings about the controversy that had surrounded the SMILE trial, and specifically discussed the following tables:

Table 1. Data taken from Action for ME (AfME) and Association of Young people with ME (AYME) joint report "M.E. 2008: What progress". 2763 people answered this survey (7% were children and young people)

Intervention	Helpful (%)	No change (%)	Made worse (%)
GET	45	21	34
CBT	50	38	12
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*GET = Graded Exercise Therapy. CBT = Cognitive Behavioural Therapy.

For the full report:
http://www.afme.org.uk/res/img/resources/Survey%20Summary%20Report%202008.pdf

Also reported in Parliamentary enquiry found here:
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Table 2. Data taken from 2008 MEA survey of 4217 people (<5% where children and young people)

Answer Options	Response count	Greatly improved	Improved	No change	Slightly Worse	Much worse
GET	906	3.4	18.7	21.4	23.4	33.1
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http://www.meassociation.org.uk/wp-content/uploads/2010/09/2010-survey-report-lo-res10.pdf

Also reported in Parliamentary enquiry found here:
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Contact / Further Information:

XXX Or if you want to talk to somebody independent please contact XXX

THANK YOU for taking the time to read this leaflet

SMILE: Interview Topic Guide

v2 May 2010

These questions will be used as prompts to ensure all important areas are covered

Welcome, introduction, stress confidentiality. Discuss consent, sign form or check continues to be happy with consent.

<u>After assessment & before randomisation</u>

1. **Can you talk me through your initial appointment with the research nurse?**
   Prompts: What was said, did you understand what was being said? Feelings?

2. **What were your initial thoughts about the study?**
   Prompts: What did you think when you were told about it? Feelings? Worries? Expectations?

3. **Did you know anything about the Lightning Process before this initial appointment (for first interview only)?**
   Prompts: How/ who? What did you think? What information?

4. **What did you think about the information you were given about the study?**
   Prompts: What information did you get – oral and written? Did you read it? Understand it? Did it give you enough information/too much? Were there things you thought they had forgotten to include?

5. **Have you found out any information about the Lightning Process since?**
   Prompts: Why? How? What did you find? What did you think?

6. **What are your thoughts at this stage on taking part or not? Why?**
   NB - Stress that they're not being asked at this stage but that we want to gauge their thoughts, stress also that it makes no difference to the interviewer

7. **If you were to take part, would you have a preference for one of the interventions?**
   Prompts: Why? Issues over participation? Engagement? What would you do if allocated the other intervention?

8. **What do you think about having treatments allocated at random, i.e. by chance?**
   Prompts: Why is it done? How do you feel about this way of deciding what treatment you'll get? Is there a better way? Do you think you'll be happy to be randomised? Do you think you're likely to get one intervention rather than the other? Why?

9. **You have now done some questionnaires at follow up. What did you/your child think about the questions you were asked?**
   Prompts: Were there any particularly difficult ones? What did you think about the HAD POMS inventory? Would you leave some out? Other areas that should be covered?

After randomisation & before interventions

1. **Can you tell me what happened when the research nurse visited and explained about randomisation?**
   Prompts: What did she say? Understandable? What did you think? Did you understand what was going to happen?

2. **What did you think before randomisation?**
   Prompts: Were you happy with the process? Did you understand what was going to happen and why?

3. **Did you agree to randomisation or not? Why?**

4. **What did you think when you got your intervention allocation?**

   Prompts: How did you feel? Was it what you expected/wanted? Expectations of intervention? What have you done since then?

5. **You have now done some questionnaires at follow up. What did you/your child think about the questions you were asked?**

   Prompts: Were there any particularly difficult ones? What did you think about HADS

   /POMS inventory? Would you leave some out? Other areas that should be covered?

After intervention

1. **Tell me about the intervention you received?**
   Prompts: What happened? What was good/bad? What would you change? Venue? Structure of sessions? Language used? Was it as expected?

2. **Do you think you/your child have/has learnt anything from it, if so what?**
   Prompts: About CFS/ME, themselves, self-management?

3. **What has happened after the intervention?**
   Prompts: How have you/they done? What are you/they doing? Feeling?

4. **What do you think now about being randomised?**
   Prompts: Would you do it again? What do you think about the study for others?

5. **You have now done some questionnaires at follow up. What did you/your child think about the questions you were asked?**
   Prompts: Were there any particularly difficult ones? What did you think about the HAD POMS inventory? Would you leave some out? Other areas that should be covered?

SMILE: Recruitment training methods

During the SMILE RCT a clinical CFS/ME team provided a brief introduction to SMILE and gaining 'consent to contact' from families at the end of the patient initial assessment appointment. The research team would then contact families to discuss the RCT in full, usually at a face-to-face meeting in their home. During the SMILE RCT rates of recruitment were not formally monitored in conjunction with recruiter training.

Initial one-to-one training sessions were provided for recruiters shortly after they joined the research team. These training sessions included informal discussions with the qualitative lead (NM) and the qualitative researcher, (LB) in relation to best practice and recruitment strategies used in the ProtecT trial. [123] Training discussions focussed on communication strategies that might facilitate informed consent, including; providing evidence-based information and emphasising the equivalence of all treatments offered in the RCT, spending a similar amount of time explaining each intervention arm, ceding the floor to allow patients/parents to express their views and preferences, and discussing preferences. An existing generic 'Tips for recruitment' document developed by the lead qualitative researcher (NM) was also given to recruiters, (see: SMILE: Tips for Recruitment and informed consent) and was used for the duration of the RCT.

During the three months after each recruiter joined the SMILE RCT, the qualitative lead provided tailored feedback to recruiters, by listening to and reviewing two randomly selected transcribed sections of their audio-recorded recruitment consultations. Verbal feedback relating to good practice was provided via informal one-to-one meetings. Recruiter questions were answered, and written feedback

notes from analyses of the audio-recordings were provided for recruiters ongoing reference. When new recruiters joined the research team they ‘shadowed’ the existing recruiter, firstly by observing a consultation, then conducting one themselves with the experienced recruiter present to provide support where required. New recruiters then went on to conduct consultations alone. Recruitment consultations were routinely transcribed and analysed so that further feedback on best practice could be provided on an ongoing basis. This training was delivered on an ad-hoc basis if qualitative researchers felt it necessary to highlight communication issues, good practice, or when recruiters requested feedback in relation to specific consultations.

SMILE: Tips for Recruitment and informed consent

Tips to facilitate trial recruitment consultations
(from the ProtecT study)

Taken from: BMJ 2002 (Donovan), JCE 2009 (Donovan), SSM 2009 (Wade), JCE 2011 (Mills)

Suggested recruitment consultation format (to adapt):

Opening – describe patient journey so far, empathise with the patient's dilemma of which treatment to choose, summarise the study and why/how it's being done (including uncertainty surrounding best treatment, why randomisation is used and how it's done), ascertain the patient's initial views on treatments and randomisation ("What are your thoughts at this stage?"), and ensure patient is aware that their needs are paramount.

Process – explain details of the process and advantages and disadvantages of treatments, explore patient's views and preferences further in light of the evidence on treatments and clinical equipoise, tailor information provision to needs.

Ending – Ensure all preferences/views have been addressed, emphasise the purpose and advantages of randomisation, obtain consent for randomisation only if patient is willing to keep an open mind towards all treatments, and ensure that if a patient has a clear preference for a particular treatment it is arranged.

Suggested approaches

1. **Ensure an accurate explanation of the purpose of the trial and randomisation early on in the consultation:**

   Do so before going into detail about each treatment then further explain after.

2. **Express uncertainty/equipoise and randomisation convincingly:**

   Emphasise that the patient is eligible for all treatments, the best treatment is not known, a trial is needed, and randomisation is a plausible way of reaching a treatment decision and can resolve the dilemma of treatment choice.

   Empathise with the patient's dilemma of which treatment to choose. Offer randomisation as a tool to aid decision-making for those who are uncertain about the treatments.

   Recruiters must be genuinely uncertain about the best treatment, believe patients to be suitable for all treatments and confident in these beliefs.

3. Consider the order and content of presentation of treatments:

Ensure equivalent proportion of time given to discuss each treatment.

Present treatments equally - describe advantages and disadvantages of treatments in equivalent detail.

Present the least favoured treatment first.

Consider the name given to the standard care arm - make it sound appealing.

Avoid terms that may be misinterpreted e.g. use 'study' rather than 'trial'.

4. Empower recruiters to elicit and address treatment preferences:

Recruiters should be confident to elicit and address patients' treatment preferences by acknowledging them, ascertaining their basis, and offering counterbalanced information in response by emphasising the position of clinical equipoise, uncertainty of prognosis, putting concerns into perspective and ensuring they understand the pros and cons of their desired and less desired treatment.

If a participant gives a view/preference try to explore fully the reasons underpinning this view – reasons are usually multilayered, complex and may be highly emotive rather than based on accurate reasoning or sound information.

Techniques to elicit patients' views/concerns include: open ended questions (eg how did you get on with the PIS?), deliberate pausing, readily concede floor if overlap of speech, and repeat questioning and probing to articulate concerns and provide tailored information to address concerns.

Attempt to balance patient's views about treatments in light of the available evidence and ensure that the patient has an open mind towards all treatments before proceeding to randomisation.

5. Informing patient of treatment allocation:

Be upbeat about the allocation – not hesitant. Emphasise the positive aspects of the treatment.

Provide details about what will happen next, rather than re-exploring treatment options.

Explore and address concerns if you feel the patient is hesitant.

Inform patients of time to consider acceptability of allocation if needed.

Recruiters need to be committed to these approaches – patients can pick up on this if not.

SMILE: Content analysis checklist

Adapted from N. Mills ProtecT (Prostate Testing for Cancer and Treatment)

Information Appointments Oct-Dec 2005.

1. Young person: Preference at outset
2. Parent: Preference at outset

Preference expressed at outset? - State 'yes' if the preference is expressed fairly early on in the consultation i.e. prior to a discussion of the two treatments. If the preference is first expressed later in the consultation then please state "Yes (but after a discussion of 1 or 2 treatments)" or whatever is appropriate.

Preference expressed at outset may also be a 'non-preferred' intervention - i.e. if they express not wanting a particular treatment. Please make this clear if so then treat as you would a preference.

3. Young person: Key reasons for preference
4. Parent: Key reasons for preference

If reason(s) for preference provided, please record.

(e.g., knew someone who had treatment in the past.)

5. Young person: Preference: definite, probable, or no evidence / preference not stated
6. Parent: Preference: definite, probable, or no evidence / preference not stated

- *'Definite'* if they repeat their preference at various points throughout the consultation and/or they have definite reasons for preferring this treatment – i.e. their initial preference seems to be quite strong/sure/grounded.

- *'Probable'* if they express a preference but then don't follow this up, seem pretty unsure, change their mind, don't give reasons for their preference etc - i.e. their initial preference seems weak/unsupported/not definite but they did single out a treatment.

- *'No evidence / preference not stated'* do not provide verbal response to questions relating to preference / preferences not explored during recruitment discussion.

7. Young person: Entrenched or dispensed with as consultation proceeds
8. Parent: Entrenched or dispensed with as consultation proceeds

Entrenched or dispensed with as consultation proceeds?

- State whether their preference is strengthened (entrenched) or weakened/dissipated/dissolved (dispensed) as a result of the discussion with the recruiter.

9. *Outcome at end of recruitment discussion* (e.g., randomised or declined randomisation)

Appendix 4: MAGENTA

*[Reference: Brigden, A., et al., Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: study protocol. BMJ Open, 2016. **6**(7): p. e011255.]*

MAGENTA: Inclusion/exclusion criteria

Inclusion criteria
Children and adolescents will be eligible for inclusion if they are given a diagnosis of CFS/ME (made using NICE guidance*) and aged between 8 and 17 years inclusive. *[*NICE: National Institute for Health and Clinical Excellence, Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) Diagnosis and management of CFS/ME in adults and children., N.I.f.H.a.C. Excellence., Editor. 2007, Developed by the National Collaborating Centre for Primary Care: London].*
Exclusion criteria
Children and adolescents will be excluded if they are severely affected. NICE defines severe CFS/ME as individuals who are unable to do activity for themselves, or carry out minimal daily tasks only, they have severe cognitive difficulties and depend on wheelchair for mobility or are referred for CBT at their first clinical assessment, or are unable to attend clinical sessions.

MAGENTA: Eligibility assessment

Eligible young people were identified by health professionals at their initial assessment appointment with the specialist CFS/ME team. Patients diagnosed with CFS/ME who met the eligibility criteria were informed about potential participation in a feasibility RCT at the end of their first clinical appointment. Families were given a brief verbal overview of the RCT, and the relevant patient and parent information leaflets were given to families who were interested in finding out more about the trial. The health professional asked families if they were willing to be contacted at a later date by a research nurse responsible for recruitment, and written assent/consent to contact was obtained from families who were willing to hear more about the trial and for this telephone discussion to be audio-recorded.

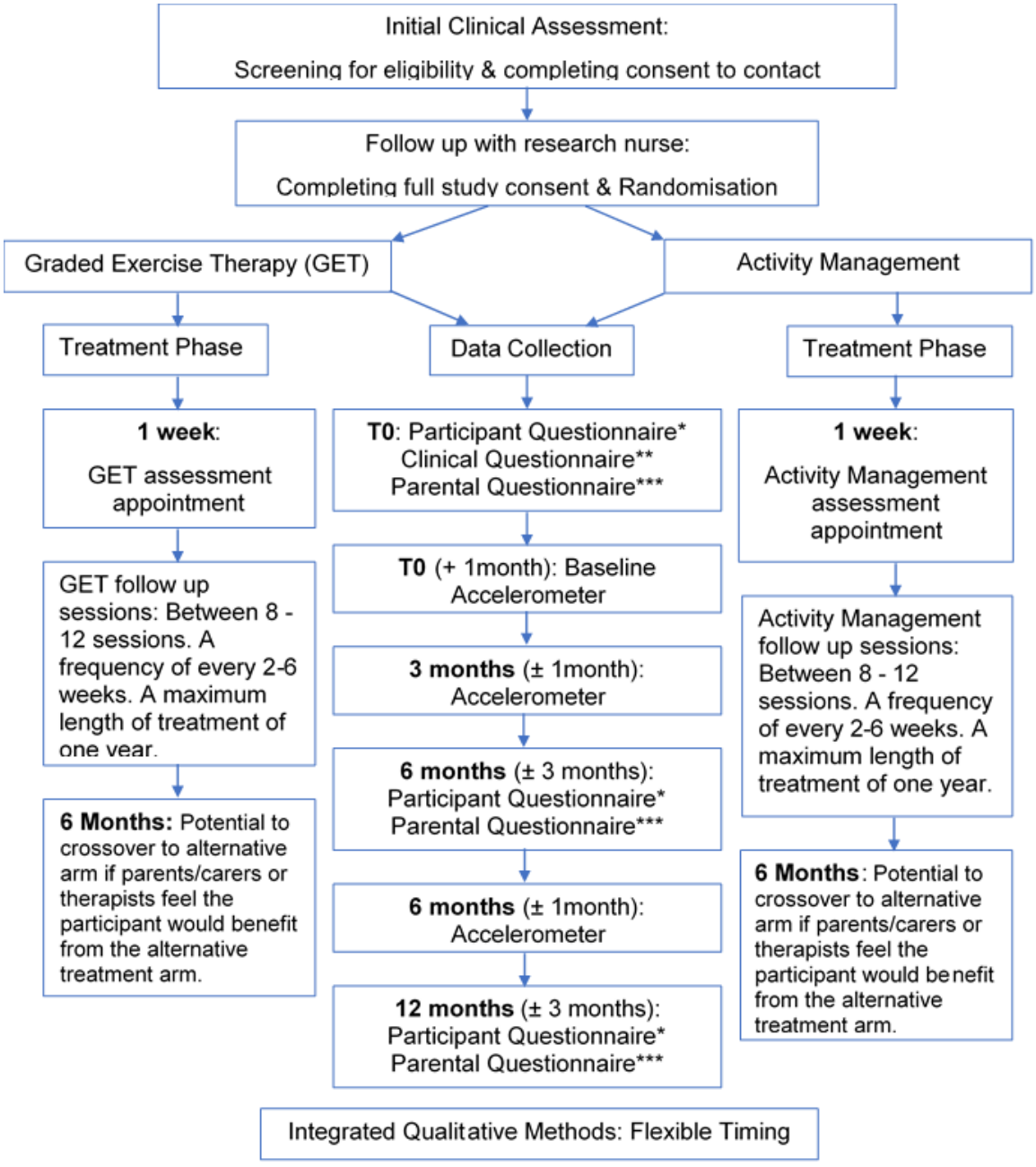
MAGENTA: Integrated qualitative aims and objectives

During the feasibility stage integrated qualitative methodology was used to assess the feasibility and acceptability of trial conduct, specifically to understand issues that would relate to the successful design and implementation of a full-scale RCT.

1. To investigate the recruitment process including eligibility assessment, the recruitment consultation and the views of children and parents, clinical and recruitment staff about the recruitment process.
2. Assess the number of eligible children, the number of children approached, the number recruited, and the number retained in the first 6 months of the study.
3. To assess issues of retention and interview those who cross-over or drop-out of the trial.
4. Assess the acceptability (satisfaction and compliance) of Graded Exercise Therapy and activity management.
5. Assess the feasibility and acceptability of using accelerometers to measure physical activity in children with CFS/ME.
6. Evaluate whether the two treatments are distinct and being delivered in a consistent manner across centres.

MAGENTA: Trial flow

Participant flow through trial related interventions and data collection procedures.



* Chalder fatigue; Physical function (SF 36); Hospital Anxiety Depression Scale; Spence Children's Anxiety Scale; Co-morbid conditions; Pain visual analogue scale; Quality of life (EQ-5D-5L)
** Age; Sex; Ethnicity; School attendance, % possible school; Symptoms List CDC & NICE criteria; Months of illness; Clinical Global Impressions scale
*** socioeconomic status (baseline only); adapted 4 item Work Productivity and Activity Impairment Questionnaire (General Health V2.0 [WPAI:GH]); adapted existing health resource use questionnaire

MAGENTA: Data collection and randomisation

Randomisation and allocation outcome

The recruiter randomised those who provided assent/consent to participate. Randomisation was carried out via a web-based randomisation system, operated by the Bristol Randomised Trials Collaboration, (telephone randomisation was used on occasions when the web-based system was unavailable). Allocation to the two treatment groups of either Graded Exercise Therapy or activity management (ratio 1:1) used minimisation to facilitate balance between treatment groups by age (categories: 8-12-years and 13-17-years) and gender. A random component was retained to prevent accurate prediction of allocation. Because of the nature of the intervention, it was not practical to blind either the family or the clinical service to treatment allocation.

Families were given their randomisation outcome either at the end of the recruitment consultation, or at an agreed time after the call on occasions when the randomisation website was not accessible. Recruiters were asked to leave the audio-recorder on until after the participant was given their group allocation, so that young person and parent reactions to the allocation was captured on the recording. After allocation the recruiter informed the clinical service of the patient's allocation, so that a letter could be sent to the family with their follow-up appointment details. The participant's GPs was also informed what intervention the young person was receiving in the MAGENTA trial.

Recording of follow-up appointment

Follow-up appointments were routinely audio-recorded by the research team to document the interaction between health care professionals and participants in receipt of Graded Exercise Therapy and activity management in the MAGENTA trial. These recordings were recorded to determine intervention fidelity and were not include in the analyses of this project.

MAGENTA: Intervention groups

Graded Exercise Therapy: Intervention Overview

Young people were offered advice that was focused on exercise with detailed assessment of current physical activity and a programme including timed daily exercise. Young people were asked to record the amount of exercise they did and were taught to use a heart rate monitor with target heart rates to avoid over-exertion. They were able to choose whether they wanted text reminders to do exercise. The exercise programme was negotiated and agreed at each appointment between the health professional, young person and parent/carer. Health professionals delivered interventions in both groups were encouraged to offer routine advice about sleep, medication use and symptom control.

Young people, their parents/carers and the health professional who provided the intervention chose the number of follow up sessions (between eight & 12) and the frequency of appointments (every two to six weeks) with a maximum length of treatment of one year. The number, frequency and length of follow up sessions for each participant was recorded, along with data on heart rate monitor use.

Participants who developed anxiety or depression that require treatment during the trial follow-up period were offered up to 12 sessions of CBT. Individual CBT sessions were delivered every two weeks by a clinical psychologist who specialised in CFS/ME. Participants were able to cross-over after six months (the primary outcome point) Participants were free to withdraw from either the intervention or the trial at any time. If participants wanted to cross-over before six months, their decision was recorded and they were asked if they would be willing to continue to provide outcome (trial) data.

GET Intervention Monitoring: Ongoing Intervention

Research ID:

Date of Appointment: 6 Month Due:

Session Number: *Please use 6-month form if applicable

Mandatory	**Tick if discussed**	**Reason if not discussed**
Has initial exercise target been achieved for everyday for 1-2weeks? if yes:		Y / N
Child advised to increase exercise slowly by 10-20% a week		
Is the child doing 30 minutes of gentle exercise each day if yes:		Y / N
Child advised to increase exercise intensity such that participants start doing aerobic exercise		
The aerobic component will then be slowly increased as the total amount of exercise is increased		
Participants will be encouraged to continue to increase exercise to achieve Department of Health recommended levels of 60 minutes a day of a mixture of moderate/vigorous intensity aerobic with muscle strengthening activities on three days/week.		
For all participants:		
Child advised to continue to time and record their exercise		
Diary reviewed to help young people ensure their exercise is the same every day		
Did the child use the diary?		Y / N
Child advised to continue to monitor their heart rate using a heart rate monitor. Target set.		
Has child been using heart rate monitor		Y / N
Managing setbacks discussed prior to discharge in the context of physical exercise (how much this		

should be reduced and when they should start to do exercise again).		

Prohibited	**Tick if discussed**	**Reason if discussed**
Advice on cognitive activity		
Discussion about the different types of cognitive activities		
Instructions to record the cognitive activities		
Flexible	**Tick if discussed**	
Assessment of range of movement.		
Advice on length of time at school (full /half days, one lesson a day) and support increasing time at school.		
Advice over exams		
Young people can be shown how to do stretches		
They can also be offered a strengthening programme if this is one of their goals		

Referred to CBT Y / N
Has an Adverse even been reported Y / N (if yes, please find adverse event form at the back of this Pack and please notify research team)

Activity management: Intervention Overview

Activity management converted a “boom-bust” pattern of activity to a manageable amount that could be achieved consistently every day (baseline). The activity management intervention in the MAGENTA RCT focused only on cognitive activities: school, school work, reading, socialising, and screen time (phone, laptop, TV, games). Those allocated to this group received advice about the total amount of daily activity, **excluding physical activity**, they did not receive specific advice about their use of exercise, increasing exercise or timed physical exercise. Health professionals delivered interventions in both groups were encouraged to offer routine advice about sleep, medication use and symptom control.

Young people, their parents/carers and the health professional who provided the intervention chose the number of follow up sessions (between eight & 12) and the frequency of appointments (every two to six weeks) with a maximum length of treatment of one year. The number, frequency and length of follow up sessions for each participant was recorded, along with data recorded on activity charts. Participants who developed anxiety or depression that require treatment during the trial follow-up period were offered up to 12 sessions of CBT. Individual CBT sessions were delivered every two weeks by a clinical psychologist who specialised in CFS/ME. Participants were able to cross-over after six months (the primary outcome point) Participants were free to withdraw from either the intervention or the trial at any time. If participants wanted to cross-over before six months, their decision was recorded and they were asked if they would be willing to continue to provide outcome (trial) data.

Activity Management Intervention Monitoring: Intervention

Research ID:

Date of Appointment: 6 Month Due:

Session Number: *Please use 6-month form if applicable

Mandatory	**Tick if discussed**	**Reason if not discussed**
Has the participants managed the baseline for 1-2 weeks?		Y / N if yes:
Increase this baseline by 10-20% each week.		
Participants will continue to increase activity until they are able to do at least 8 hours of cognitive activity a day.		
All participants:		
The different types of cognitive activity (high concentration and low concentration) which will vary according to age Cognitive activities include time at school or doing school work, reading, some craft/hobbies, socialising and screen time (phone, laptop, TV, computer, other devices)		
Advise participants to record the total number of minutes spent each day doing high-energy cognitive activities using paper diaries/ “ActiveME” app. Recording activity is used to help participants understand whether they are doing the same each day or varying their activity and whether the baseline has been set at the correct level.		
Therapists will discuss problems encountered by participants and provide possible solutions. Managing setbacks will be discussed (how much to reduce school and other cognitive activity and for how long).		
Prohibited	**Tick if discussed**	**Reason if discussed**
Discussion about number of steps, minutes of exercise etc.		
Aerobic, versus non-aerobic activity		
No discussion about increasing physical activity (only discussion about increasing overall activity)		
No advice on exercises or using a strengthening programme		

Flexible	**Tick if discussed**	
Advice on PE in school (no PE, half a lesson, full lesson)		
Attendance at sporting events (do not attend, attend limited period of time)		
Young people can record physical activity within the total cognitive activity but are not required to do so		

Referred to CBT Y / N
Has an Adverse even been reported Y / N (if yes, please find adverse event form at the back of this Pack and please notify research team)

MAGENTA: Information leaflet for young people (8-11yrs)

v0.6 30/03/2015

MAGENTA

Managed Activity Graded Exercise iN Teenagers and pre-Adolescents

Information leaflet for children aged 8-11 years

We would like to invite you to take part in a research study which will tell us if we can find out whether one type of treatment for CFS/ME works compared to another treatment.

Please read this carefully. You can talk about it with your family, friends, doctor, or us

Ask us if there is anything you don't understand.

Take time to decide whether or not you want to join in.

Thank you for reading this!

Why have I been asked to take part?

We are asking you to take part because you have CFS/ME and you come to our service.

Do I have to take part?

You do not have to take part in this study. It is up to you. Your parents or your carers can help you decide. You can stop at any time.

If you decide you don't want to take part you can still use the CFS/ME service as usual.

Why are we doing this study?

We want to know which treatment is better – Activity Management or Graded Exercise Therapy for children with CFS/ME.
We want to know if children want to take part in our study and the best way to ask children to take part.
If you decide to take part we will ask you to do either Activity Management or Graded Exercise Therapy.

What will happen if I take part?

Part 1 – finding out about the study

A doctor at your CFS/ME centre will tell you a little bit about the study and invite you to take part. If you are interested in the study, the doctor will ask a nurse to speak with you and your parents/carers to give you more information.

When you speak with the nurse, the nurse will ask if they can record the conversation. You can ask the nurse any questions you have.

When you have heard all of the information and asked any questions, you will be asked if you would like to take part in the study. You can go home and think about it with your parents/carers.

Part 2 – taking part in the study

All children will have treatment for their symptoms such as pain and all children will get help with their sleep. We will ask you to fill out questionnaires (like the ones you filled in already) in 6 months and 12 months time.

We will also ask you to wear something called an "accelerometer". This is very small and measures your exercise. You only have to wear this for a week at the start, at 3 months and 6 months.

We need the groups to be the same to make the study fair. That means that a computer will decide which treatment you have, a bit like rolling a dice for a game. Your nurse or doctor, or you or your parents cannot decide.

One group is called **Activity Management**. If you are in this group we will mainly be helping you do the same amount of total activities each day. This will mainly be thinking activities like school work, seeing friends, reading and spending time on the computer.

The other group is called **Graded Exercise Therapy.** If you are in this group we will mainly be helping you manage the amount of exercise you do each day.

If you decide that you don't want to take part at any point, that is ok, and you don't have to say why.

What might be hard about taking part?

If you take part you will need to fill out questionnaires like the ones you did in the clinic which might take a little bit of time and effort. We might ask you to talk to a research nurse about the study.

We don't know if the treatment you have will make you feel better. You might feel better or you might feel the same, or you might feel worse.

What are the good things about taking part?

Some children like taking part in research because they know it will help children in the future.

What will happen when the study stops?

After the study stops, you will continue to get the same help from your CFS/ME service if you still need it. Research can take quite a long time to complete, but if you give us an email address we will write to you and let you know what we find out when we finish the study.

What will happen to all of the information about me?

All of the information you tell us will be kept private. Your name will be replaced by a number on the documents we keep about you so that you cannot be identified from them.

We will look at all of the information you and other children have given us and write about it to help other doctors help more children with CFS/ME.

What if there is a problem?

We will try and help with any problems you may have. If you get upset we will make sure someone helps you.

All of the researchers involved in the study have had special checks for working with children.

You, or your parents/carers can talk to Dr Esther Crawley who is organising the study by calling 01225 465 941 or emailing esther.crawley@bristol.ac.uk.

THANK YOU for reading this leaflet!

University of BRISTOL

NHS National Institute for Health Research

Royal United Hospitals Bath NHS NHS Foundation Trust

MAGENTA: Information leaflet for young people (12-17yrs)

v0.8 17/05/2015

MAGENTA

Managed Activity Graded Exercise iN Teenagers and pre-Adolescents

Feasibility and acceptability randomised controlled trial

Information leaflet for young people 12-17 years

We would like to invite you to take part in a research study which will tell us whether we can study the effects of Graded Exercise Therapy (GET) compared to Activity Management for Chronic Fatigue Syndrome or Myalgic encephalopathy (CFS/ME) in young people

Before you decide whether you would like to take part, it is important for you to understand *why* the study is being done and *what* it will involve. The leaflet is divided in to two parts. Part 1 tells you about the study and what will happen if you choose to take part. Part 2 gives details about how the study will be run.

Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us.

Ask us if there is anything you don't understand or if you want more information.

Take time to decide whether or not you want to join in.

Thank you for reading this!

PART 1

Why are we doing this study?

We want to test whether a treatment that we use for CFS/ME called "Graded Exercise Therapy" is effective and value for money. We want to compare this with "Activity Management" which we also use for CFS/ME.

Before we do this, we need to know whether a trial of the two treatments is possible and whether young people will take part. This study will find out whether a trial is possible.

We also want to find out more about Graded Exercise Therapy and Activity Management and whether young people like you think they are "OK" treatments.

As part of this study, we will also try and measure the cost of each treatment.

Why have I been asked to take part?

You have been asked to take part in this study because you are aged between 8 and 17 years and have a diagnosis of CFS/ME from the CFS/ME specialist unit.

If you are not able to attend your CFS/ME hospital appointments (e.g. you cannot leave the house), or any of the appointments required for the research study, we do not feel you should take part.

Do I have to take part?

You do not have to take part in this study. If you agree to meet the research nurse, they will explain more about the study. This will not commit you to taking part.

If you think that you might not want to take part in any of the activities or treatments in this, you should not enter the study.

We hope that up to 100 young people and their parents/carers will take part in this study but it is up to you to decide whether or not you would like to take part.

If I agree to take part can I change my mind?

Yes. If you decide you would like to take part but change your mind later, we will continue to follow you up like we do other young people who are not part of the study unless you tell us you don't want us to.

You can leave the study at any point and if you would like us to, we will take out the information collected about you at any point before we carry out data analysis.

If you leave the study at any time, this will not affect the standard of specialist medical care you will receive.

What will I be asked to do if I take part?

First stage:

If you would like to hear more about the study, the doctor will ask a research nurse to arrange a time to talk to you. You can do this in the clinic or on the telephone. The research nurse will explain the study to you and your parents/carers and answer any questions you may have. This discussion will be audio-recorded with your permission and will last about 30 minutes, but you can talk for longer if you have more questions. The research nurse might ask you about how you felt when the doctor asked you to take part in this study.

If you want to take part in the study, you will be asked to fill in an assent or consent form to show us that you agree. You can do this at home and post it to us, (we will provide a stamped addressed envelope) or you can email it to the research nurse or fill in a consent form on-line.

If you take part in this study, we need to make sure that those in both groups are matched. This is the only way we can compare the groups and make sure the study is fair. You will therefore be given either group 1 (Activity Management) or group 2 (Graded Exercise Therapy) at random. Half of those taking part in the study will have group 1 and half will have group 2. Your chance of getting either group is 50%. These are both treatments we currently use in our service and lots of children have already tried them.

Second stage:

In the second stage you of the study you will have treatment for your CFS/ME. **Both** groups will be seen in the specialist service and you will get lots of advice about how to improve your sleep and you will get treatment for your symptoms. With your permission we would like to audio-record these sessions. We will probably see you 8-12 times in clinic.

We will ask you to wear an accelerometer to measure exercise at 3 times: at the beginning and 3 and 6 months later. This is a small box that you will wear on a band around your hips. Lots of young people have used these to measure exercise. We may ask you to record when you wear it and when you take it off.

We want to find out more about what you think about this study. A researcher may ask to meet with you and your parents/carers to find out what you think about the study or the treatments. This discussion will be audio-recorded with your permission, we will only discuss the study with you once for about 30 minutes.

In addition, you will get either Activity Management (group 1) or Graded Exercise Therapy (group 2).

Group 1: Activity Management

If you are in this group, you will have a detailed assessment of the activity you do. This includes thinking activity such as school work, homework, time on the computer and screens, reading and hobbies that require concentration and physical activity such as walking or PE. We call this high energy activity. We will ask you to record your activity on paper or our

iPhone app "ActiveME". We will then help you find your "baseline" activity which is the average amount of activity that you can do each day. When you have found your baseline activity, we will help you increase this by 10-20% each week. This is called activity management.

Group 2: Graded Exercise Therapy

If you are in this group, you will receive a detailed physical assessment including how far you can walk in 2 minutes and how many times you can move from sitting to standing in one minute. This will help us set a safe exercise programme. You will be asked about the exercise you do each day and will be helped to find you exercise baseline. The baseline is the average amount of exercise you do each day. It will be less than you do on a good day. When you have found your baseline, we will ask you to slowly increase you exercise. When you are able to do 30 minutes each day, we will increase the intensity of your exercise. You will be asked to record exercise using either charts or the iPhone app ActiveME. You will not be asked to record other activities, only your exercise. To make sure you do not over do your exercise, we will ask you to use a heart rate monitor.

What is the difference between Group 1 and Group 2?

Activity Management will mainly be working on activities that take up most of the day like school work. It does not focus on exercise or include a physical assessment or heart rate monitoring. Graded Exercise Therapy gives detailed advice about exercise with an assessment of your exercise and uses a heart rate monitor. Graded Exercise Therapy will not ask you to monitor other activities such as school work.

Are there any disadvantages to taking part in this study?

You will need to spend time talking to a doctor for about 10 minutes, so we can understand if you are interested in the study. You and your parents/carers will need to arrange a time to meet or talk (on the phone) to a research nurse about the study. This will take about 30 minutes.

If you take part, you and your parents/carers will need to complete questionnaires at 6 months and 12 months. We ask all young people to complete these questionnaires. These questionnaires will take you about 20 minutes.

You may not find the treatment you are offered helps you. Young people with CFS/ME can get worse even with the treatment offered and we do not know how many will get worse (or better) with either Activity Management or Graded Exercise Therapy. This is why we are doing a study. If you do not find the treatment helps you, you can have the other treatment after 6 months.

Will I experience any side effects from taking part in this study?

We have used both treatments in our service and we are not aware of side effects. Studies in adults have also not shown that there are any side effects from these treatments.

What are the benefits of taking part in this study?

You may feel better from the treatment you are undergoing, but we cannot say this for certain. You may learn something about how a research trial works. Some young people with CFS/ME like to know that they are helping others with CFS/ME in the future.

What will happen when the study stops?

After the study stops, you will continue to access specialist medical care if you still need it. You will also continue to receive follow up questionnaires, like the young people who did not take part in the study. If you want to know the study results, let us know and we can send them to you.

PART 2

If you are still interested in taking part in the study, please read the information below before making your decision.

Assent and consent

We have to be absolutely certain that you are happy to join this study. We will ask you to sign an assent form (if you are 12-15 years old) or consent form (if you are 16-17 years old). We will also ask you to sign one of these forms if we record treatment sessions or discussions. Even if you do sign the forms, you will be free to stop the recording or leave the study at any point. Just tell us if this is the case. Whether or not you wish to take part, you will continue to receive the same care from the clinical team.

What will happen to the information you collect about me?

It is very important that all the information you give us is completely private. The conversations that you say we can record will be encrypted and password protected (so no-one else can listen to them). They will be stored on a secure University of Bristol server.

We only use a research code to identify you. No name or personal information will be on the questionnaires we send you. All personal details that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS or University of Bristol computers.

We may use some of the things you say when we write about the study but we will take your name and any other information off so no one will know who was speaking.

We would also like to keep the things you say so that other researchers can use it for research and teaching now, and in the future. We will check you are happy for us to use the things you say in this way.

If you tell us something that makes us worried about your safety, we may have to discuss this with somebody else as we need to be sure you are safe. This means, what you say would not be kept completely private. We would do the same if you told us something in clinic.

Does everybody involved in the study have the right police checks?

Yes. All those working in the study have had police checks to make sure they are safe to work with children and young people.

Who will know that I am taking part in the study?

We think your GP should know that you are taking part in this so we will write to your GP to tell them which treatment you will be receiving in the study.

What will happen to the results of the study?

This study will give us information about how effective Graded Exercise Therapy and Activity Management are. This study will also tell us if young people are interested in taking part in this research. We aim to publish these results in journals to help other people treating young people with CFS/ME. If young people take part in this study, we will use the results to plan for a larger study to look at whether Graded Exercise Therapy or Activity Management is useful for young people.

What if new information becomes available whilst I am in the study?

If new information becomes available, we will tell you about it and discuss whether you want to continue in the study.

Who is organising and funding the study?

This research is organised by Dr Esther Crawley who leads the Bath specialist CFS/ME service and the CFS/ME Research team at the University of Bristol.

The study is funded by the government's research fund - the National Institute of Health Research (NIHR) and is sponsored by The Royal United Hospitals (RUH) Bath NHS Foundation Trust. This research is organised by Dr Esther Crawley who leads the Bath specialist CFS/ME service and the CFS/ME Research team at the University of Bristol.
The study is funded by the government's research fund -the National Institute of Health Research (NIHR) and is sponsored by The Royal United Hospitals (RUH) Bath NHS Foundation Trust.

What should I do if I have a problem with this study?

If you have any problems with this study, please speak to your parents/carers, Dr Esther Crawley, or any member of the clinical team that you know. Dr Crawley's contact information can be found at the end of this information.

You can also complain to the NHS in the usual way through the Patient Advice and Liaison services (PALS) 01225 473424.

Will I need to pay to be part of this study?

No.

Ethical approval

Ethical approval means that this study is safe to carry out on young people. The study has been approved by the National Research Ethics Service Committee South West – Frenchay REC.

Who can I contact for further information?

Address:

Tel:

Email:

Address:

Tel:

Email:

THANK YOU for taking the time to read this leaflet!

University of BRISTOL

NHS National Institute for Health Research

Royal United Hospitals Bath NHS
NHS Foundation Trust

MAGENTA: Information leaflet for parents

v0.7 17/05/2015

MAGENTA

Managed Activity Graded Exercise iN Teenagers and pre-Adolescents

Feasibility and acceptability randomised controlled trial

Information leaflet for parents/carers

We would like to invite your child to take part in a research study which will tell us whether it is possible to study the effects of Graded Exercise Therapy (GET) compared to Activity Management for Chronic Fatigue Syndrome or Myalgic encephalopathy (CFS/ME) in young people aged 8 to 17 years.

Before you decide whether you would like your child to take part, it is important for you to understand *why* the study is being done and *what* it will involve. The leaflet is divided in to two parts. Part 1 tells you about the study and what will happen to your child if you choose for them to take part. Part 2 gives details about how the study will be run.

Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us

Ask us if there is anything you don't understand or if you want more information.

Take time to decide whether or not you want to join in.

Thank you for reading this!

PART 1

Why are we doing this study?

We want to compare a treatment that we use regularly for children with CFS/ME called "Graded Exercise Therapy (GET)" with another treatment called "Activity Management". We want to see if GET is effective and value for money. Before we do this, we need to know whether a trial is possible and whether young people will take part. We want to know whether young people think the treatments are acceptable and how much the treatments cost. This will help us understand if a trial is possible.

Why has my child been asked to take part?

Your child has been asked to take part in this study because they are aged between 8 and 17 years and have a diagnosis of CFS/ME from the CFS/ME specialist unit. If you feel that your child is will not able to attend hospital appointments because they cannot leave the house this would mean they should not take part. If you would not want your child to take part or receive one of the treatments in this study, you should not allow your child to enter the study.

Does my child have to take part and can I change my mind?

Your child does not have to take part in this study. If you and your child agree to meet the research nurse who will explain more about the study, this will not commit your child to taking part in the study.

If you decide you would like your child to take part but change your mind later, we will continue to follow your child up like we do other young people who are not part of the study unless you tell us you don't want us to. You can withdraw your child from the study at any point.

We hope that up to 100 young people and their parents/carers will take part in this study but it is up to you to decide whether or not you would like your child to take part. If you decide you would not like you child to take part or decide to withdraw your child at any time, this will not affect the standard of specialist medical care your child will receive.

What would we ask you and your child to do?

First stage:

A clinician at your specialist CFS/ME centre will invite you and your child to take part in this study. They will briefly describe the study and give you an information pack. If you would like r further information, the clinician will give your contact details to a research nurse who will arrange a time to discuss the study with you and your child at the CFS/ME centre or on the telephone.

The research nurse will explain the study and answer any questions you may have. This discussion will be audio-recorded with your permission and will last about 30 minutes but you can talk for longer if you have more questions. The research nurse may ask you and your child about how you felt when the clinician asked you to take part in this study.

If you and your child agree to take part in the study, you will be asked to fill in a consent form to confirm this. You can do this at home and post it or email it to us or give it to the research nurse or fill in the form on line.

If you child takes part in the study, we need to make sure that both groups are matched as this is the only way we can compare groups and make sure the study is fair. You child will be randomly allocated (in other words, by chance) to one of two groups: either Activity Management or Graded Exercise Therapy. As this study is trying to find out whether we can compare both groups, it will not be possible for you to choose the group for your child.

Second stage:

In the second stage of the study your child will have treatment for their CFS/ME. Children in both groups will be seen regularly in the specialist service and receive assessment and treatment for symptoms and sleep. With your permission we would like to audio-record these sessions. We think they will probably be seen 8-12 times but you will be able to decide how often and for how long.

Children in both groups will be asked to wear an accelerometer. This is a small box that they will wear on a band around their hips. Lots of young people have used these to measure exercise. We may ask your child to record when they wear it and when they take it off.

We want to find out more about what you and your child think about this study. A researcher may ask to meet with you and/or your child to find out what you think about the study or the treatments. With your permission we would like to audio-record these discussions; we will only discuss the study with your child once for about 30 minutes.

In addition, your child will get either Activity Management (group 1) or Graded Exercise Therapy (group 2)

Group 1: Activity Management

If your child is in this group, they will have a detailed assessment of the total activity they do each day. This will mainly be thinking activity such as school work, homework, time on the computer and screens, reading and hobbies that require concentration. It will also include the amount of time spent doing physical activity such as walking or PE but we will not ask for any detail of exercise or for this to be recorded separately. We call all of this “high energy activity”. We will ask your child to record this on paper or our iPhone app “ActiveME”. We will then help them find their “baseline” activity which is the average amount of activity that they do each

day. When your child has found their baseline, we will help them increase their activity by 10-20% each week.

Group 2: Graded Exercise Therapy

If your child is in this group your child will receive a detailed physical assessment including how far they can walk in 2 minutes and how many times they can move from sitting to standing in one minute. This will help us set a safe exercise programme. Your child will be asked about the exercise they do each day and will be helped to find their exercise baseline. The baseline is the average amount of exercise they do each day. It will be less than they do on a good day. When they have found their baseline, we will ask them to slowly increase their exercise. When they are able to do 30 minutes each day, we will increase the intensity. They will be asked to record exercise using either charts or the iPhone app ActiveME. They will not be asked to record other activities, only their exercise. To make sure your child does not over do the exercise, we will ask them to use a heart rate monitor.

What is the difference between Group 1 and Group 2?

Activity Management will work on the total amount of activity done each day. This is mainly thinking activities. It does not provide specific advice about exercise include a physical assessment or heart rate monitoring. Graded Exercise Therapy provides specific advice about exercise with a physical assessment and uses heart rate monitoring.

Are there any disadvantages to my child taking part in this study?

You and your child will need to spend time talking to a clinician for about 10 minutes and a research nurse for about 30 minutes to understand about the study. If you take part, you and your child will need to complete questionnaires at 6 months and 12 months after starting the study. We ask all children to complete these questionnaires. We will also ask you to complete questionnaires so we can measure the cost of treatment. These questionnaires will take you about 20 minutes.

Treatments for CFS/ME don't help everybody and you may find the treatment your child has been offered does not help them. This could be true for both treatments. Young people with CFS/ME can get worse with any intervention offered and we do not know how likely this is. If your child does not get better with the treatment, they can have the other treatment after 6 months if they want it.

Will my child experience any side effects from taking part in this study?

We have used both treatments in our service and we are not aware of side effects. Studies in adults have also not shown that there are any side effects of these two treatments.

What are the benefits of my child taking part in this study?

Your child may benefit from the treatment they receive, but we cannot guarantee this. Some children with CFS/ME like to know that they are helping other children in the future. Your child may also learn about research.

What will happen when the study stops?

After the study stops, your child will continue to have specialist medical care if they still need it. Your child will also continue to receive follow up questionnaires, like the young people who did not take part in the study.

Research can take quite a long time but if you give us your email address, we will write to you and let you know what we find out when we finish the study if you are interested.

PART 2

If you are considering your child taking part in this study, please read the additional information below before deciding.

Consent

We have to be absolutely certain that you are happy for your child to join in this study, so if you say you are, we will ask you to sign our consent form. We will also ask you to sign a consent form if your child is aged between 8 -15 and we discuss the study with them. Even if you do sign the forms on behalf of your child, you will be free to withdraw your child at any point. Just tell us if this is the case. Whether or not you wish your child to participate, your child will continue to receive the same care from the clinical team.

Your privacy and data protection

It is very important that all the information you give us is completely private. The conversations that you have given your permission to be recorded will be encrypted and password protected (so no-one else can listen to them). They will then be stored on a secure University of Bristol server.

We will only use a research code to identify your child on data. No name or personal information will be on the questionnaires we send out to you or your child. All personal details that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS or University of Bristol computers.

Quotes from conversations will be used when results are published but the names of the people quoted will not be used so no one will know who was speaking. We would like to keep anonymised data and quotes collected during the study so that the University of Bristol's School of Social and Community Medicine can use it for research and teaching purposes now, and in the future. We will ask you to tell us if you are happy for us to them in this way.

If you tell us something that makes us worried about yours or your child's safety, we may have to discuss this with somebody else as we need to be sure you are safe. This means, what you say would not be kept completely private. We would do the same if you told us something in clinic.

Does everybody involved in the study have the right police checks?

Yes. All those working in the study have had the necessary police checks to make sure they are safe to work with children and young people.

Who will know that my child is taking part in the study?

We think your child's GP should know that they are taking part in this study because they need to know what happens to your child. We will write to their GP to tell them which treatment they will be receiving in the study.

What will happen to the results of the study?

This study will tell us if we can do a trial which will test how effective Graded Exercise Therapy is compared to Activity Management. It the study is possible, we will then go on to the full trial. The full trial will show us if Graded Exercise Therapy works or doesn't work. It will also tell us if it is good value for money or not. If possible, we will use the results from children involved in this study in the full trial.

What if new information becomes available?

If new information becomes available, we will tell you about it and discuss with you whether you want to continue in the study.

Who is organising and funding the study?

This research is organised by Dr Esther Crawley who leads the Bath specialist CFS/ME service and the CFS/ME Research team at the University of Bristol. The study is funded by the governments research fund the National Institute of Health Research (NIHR) and is sponsored by The Royal United Hospitals (RUH) Bath NHS Foundation Trust.

What should I do if I have a problem with this study?

If you have any problems with this study, please speak to Dr Esther Crawley or any member of the clinical team. Dr Crawley's contact details can be found at the end of this leaflet.

In the event that something does go wrong and your child is harmed during the research and this is due to someone being careless then you may be able to take legal action to get repayment from the hospital but in this case, you may need to pay a lawyer to help you. You can also use the normal National Health Service system for complaints: Patient Advice and Liaison services (PALS) 01225 473424.

Will I need to pay for my child to be part of this study?

No.

Ethical Approval

Ethical approval means that this study is safe to carry out on young people. The study has been approved by the National Research Ethics Service Committee South West – Frenchay REC.

Contact / further information:

Address:

Tel:

Email:

Or if you want to talk to somebody independent please contact:

Address:

Tel:

Email:

THANK YOU for taking the time to read this leaflet

University of BRISTOL

NHS National Institute for Health Research

Royal United Hospitals Bath NHS Foundation Trust

MAGENTA: Interview Topic Guide

v0.1 16/09/2015

Possible questions for parents/carers/young people.

We will undertake in-depth discussions with young patients and their parents/carers to understand their views and experiences of trial processes.

Discussions will take place at 2 time points: After randomisation/before intervention & during the intervention.

Ice breaker:

1. **Can you talk me through [Name's] initial appointment with the specialist service?**
   Prompts: What was said, did you understand what was being said? Feelings?

Provision and acceptability of patient information & recruitment process:

2. **What were your initial thoughts about the research study?**
   Prompts: What did you think when you were told about it? Feelings? Worries? Expectations?

3. **What did you think about the information you were given about the study?**
   Prompts: What information did you get – oral and written (PIS)? Did you read it? Understand it? Did it give you enough information/too much? Were there things you thought they had forgotten to include?

4. **Can you talk me through the conversation you had with the research nurse?**
   Prompts: What was said, did you understand what was being said? Feelings?

5. **What did you find out about activity management from the research nurse?**
   Prompts: What did she say? What did you already know? When/Where did you find this out? What did you think?

6. **What did you find out about graded exercise therapy from the research nurse?**
   Prompts: What did she say? What did you already know? When/Where did you find this out? What did you think?

7. **Can you tell me what you thought when the research nurse explained about randomisation?**
   Prompts: What did she say? Understandable? What did you think? Did you understand what was going to happen next?

8. **What did you think when you were told you got [AM/GET]?**
   Prompts: How did you feel? Was it what you expected/wanted?

Reasons for accepting or declining participation:

Use depending on whether or not the family declined or accepted to take part in MAGENTA.

9. **What did you think about having treatments allocated at random, i.e. by chance?**
   Prompts: How do you feel about this way of deciding what treatment you get? Were you happy to be randomised? Did you wonder why this is done? Is there a better way? Did you think you were likely to get one treatment rather than the other? Why?

10. **What did you think about when deciding whether or not to take part in the study?**
    Prompts: Feelings? Expectations? Worries? Treatments offered? Randomisation? What did you already know? Favoured a particular treatment?

11. **Why did you choose [not] to take part in the study?**
    Prompts: Feelings? Expectations? Worries? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know?

12. **Why did you decide [not] to accept the [intervention] allocated to [name] at randomisation?** Feelings? Expectations? Worries? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know?

13. **Why did you decide to stop participating in the study [drop-out] after randomisation?**
    Feelings? Expectations? Worries? Treatments offered? Randomisation?
    Favoured a particular treatment? What did you already know?

Acceptability of GET/AM:

14. **What do you think about the treatments [GET/AM] offered in this study?**
    Prompts: What would you have done if allocated the other treatment? Issues over participation? Engagement?

15. **Tell me about the [GET/AM] you are receiving?**
    Prompts: What has happened? What is good/bad? What would you change? Structure of sessions? How is it explained to you? Is it as you expected? Is it age appropriate?

16. **What has happened next?**
    Prompts: How are you/they doing? What are you/they doing? Feeling? Expectations? Worries?

17. **Tell me about the effect that GET/AM has had on you/your child?**
    Prompts: Their CFS/ME, themselves, self-management? School? Life in general?

Acceptability of the use of the accelerometer:

18. **What were your initial thoughts about using an accelerometer?**
    Prompts: How do you feel about wearing it? How do you find using it? Is it age appropriate? Any technical problems? Any benefits? Worries? Visibility?

19. **Are there any things we need to consider for people your age when using it?**
    Prompts: How did using the accelerometer make you feel?

Acceptability of the use of the heart monitor [GET only]:

20. **What did you think about using a heart monitor/taking your pulse?**
    Prompts: Feelings? Worries? Expectations? Do you think using the heart monitor/taking your pulse increases/decreases your/parent worries/anxiety?

And finally:

21. **What do you think now about being involved in the MAGENTA study?**
    Prompts: Would you do it again? Would you recommend it to a friend of they had CFS/ME? What do you think about the study for others your age?

22. **Is there anything else you would like to tell me?**
    Prompts: About the study? Randomisation? Taking part in research in general?

    Thank you for taking part in the MAGENTA study!

Example change to preference question:

From: SMILE topic guide (parents/young people)

If you were to take part, would you have a preference for one of the interventions?

Prompts: Why? What would you do if allocated the other intervention? Issues over participation? Engagement?

To: MAGENTA (parents/young people)

What were your initial thoughts about the research study?

Prompts: What did you think when you were told about it? Feelings? Worries? Expectations?

What did [recruiter] tell you about the treatments?

Prompts: What did she say? What did you already know? When/Where did you find this out? What did you think? Depending on which treatment they talk about first: What did [she] mention about the other [AM/GET] treatment?

MAGENTA: Recruitment training methods

During the MAGENTA RCT three clinical CFS/ME teams provided a brief introduction to MAGENTA and gaining 'consent to contact' from families at the end of the patient initial assessment appointment. Research nurses would then contact families to discuss the RCT in full via telephone. Research nurses conducted all recruitment consultations and took online consent/assent when families wished to participate in the RCT. Members of the research team carried out recruitment consultations only when research nurses were on leave.

Initial training sessions were informed by methodology developed in the QRI intervention (see: Section 2.2 Qualitative research and adult randomised controlled trials). [408] Good practice from the SMILE RCT also informed initial MAGENTA training sessions, and a structured approach to training was undertaken prior to the MAGENTA trial opening to recruitment. All initial training sessions lasted approximately 1.5 hours and were led by the qualitative researcher (LB). Initial face-to-face (site 1) or telephone (sites 2 and 3) training sessions were carried out with recruiters on a one-to-one basis. Recruiters were also provided with a training pack prior to recruitment:

1. A list of questions about confidence and recruiting to RCTs. [691]
2. Key points for difficult trials. [692]
3. Mills 2014 peer reviewed article. [247]
4. 'Tips for Recruitment and informed consent' document.

The 'Tips for Recruitment' document (see: MAGENTA: Tips for recruitment and informed consent) provided tailored information specific to communicating information about the MAGENTA RCT. It was split into four sections to support

discussion of: the study, procedures, randomisation, and included a recruitment checklist outlining key points to cover in the recruitment consultation (e.g. right to withdrawal and data protection). Because some recruiters had no experience of recruiting to RCTs, role-play 'practice' recruitment consultations were also conducted prior to the RCT opening to recruitment. Role play consultations were conducted via telephone between the trainer (LB) and recruiters, with the trainer acting as a parent or participant.

MAGENTA trial rates of recruitment were then monitored on a monthly basis, (see: The impact of communication training on recruitment figures) in conjunction with monthly trial management group meetings and ongoing training and analyses of audio-recorded recruitment consultations. Analyses of recruitment consultations was conducted by the qualitative researcher (LB) on an ongoing basis, with support from the qualitative lead (NM). Feedback was provided for recruiters during three further training sessions, (site 1 only, conducted by LB) during months three, six and 12 of the RCT. The final training session was delayed until month twelve because the CFS/ME at site 1 service moving to a new location in month 11 of the feasibility RCT. Follow-up training included examples from previous months audio recruitment consultations. Examples included good practice, and areas where changes could be made to improve communication and the process of informed consent. Written feedback was provided for recruiters, should they wish to refer to it at a later date.

The MAGENTA 'Tips for Recruitment' document was developed further in month six, to incorporate findings from analyses of recruitment consultations and feedback from recruiters. Further information was added highlighting key aspects of each RCT intervention:

Activity Management (AM): • - Assessment of cognitive activity: high concentration, low concentration (e.g. school work, screen time & hobbies) • - Find activity baseline & slowly increase activity (by 10-20% each week) • - Complete paper diaries / ActiveME app • - Focus: daily cognitive activities, no detailed discussion of physical activities
Graded Exercise Therapy (GET): • - Assessment of physical activity: how far they can walk in 2 minutes (e.g. range and type of exercise used) • - Find exercise baseline & slowly increase their exercise (by 10-20% each week) • - Complete paper exercise diaries / ActiveME app • - Child taught to monitor their heart rate • - Focus: daily exercise, no detailed discussion of cognitive activities

The following text was added to remind recruiters to highlight the lack of evidence base, because some families believing that activity management already had an evidence-base but graded exercise therapy did not:

> *"Reassure the family that these two treatment routes can be used to treat CFS/ME, are currently used by the specialist service but we need to carry out a study to develop an "evidence base so we know which one is most effective/better"*

MAGENTA: Tips for Recruitment and informed consent

V2.0 16/12/2015

University of BRISTOL

MAGENTA: Managed Activity Graded Exercise iN Teenagers and pre-Adolescents

Tips for recruitment and informed consent

This document includes suggestions that may help with recruitment and informed consent to the MAGENTA study. You may wish to consider using these suggestions alongside your own individual style.

- Please audio-record all discussions with patients, providing they are happy for you to do so. This gives us an insight into what works so we can help you and others to recruit effectively.
- Please read out the patient 'Consent ID' and the date at the beginning of each recording.

Discussing the study

- Establish uncertainty *('We don't know which treatment is best for children/young people with CFS/ME. Because we don't know which is best, we're doing a study called MAGENTA.*
  - Be mindful to convey equipoise throughout
- It works well to request patients to 'keep an open mind' until all information is heard
- Avoid the term 'trial' and use 'study' instead
- Present the study in an enthusiastic and straight-forward manner
- You can explain the benefits of study participation (e.g. *'we are doing a feasibility study to help us decide if it is possible to do a larger study comparing these two treatments so that future patients will not have to face the current treatment uncertainties'*).

Discussing the procedures

- Provide an outline of each treatment. Emphasise that both treatments are currently used in our specialist service and lots of children/young people have already tried them.
  - *'At [centre], both activity management and graded exercise therapy are good and standard approaches for the treatment of CFS/ME, but we don't know which one is better'*
- Present balanced information about both treatments
  - Spend equal time discussing the benefits and drawbacks of each
  - Avoid loaded terminology (e.g. *'gold standard', 'experimental', 'the first/second treatment'*)
- Elicit and address patients' concerns/preferences
  - An indirect, open question early on will elicit concerns or preferences *(e.g. 'What were your thoughts when you first heard about the study?')*
  - Gently find out the reasons why a patient prefers/is concerned about one option over the other. This will enable you to correct any misunderstandings and ensure they understand both treatments well enough to make an informed decision. Tailor information to the patient and/or parent individual concerns.
  - Remind the patient at the end of the discussion that regardless of which treatment they are allocated to, they will be treated with the best possible care and the health professional treating them will be experienced in that technique.

Randomisation

- It is best to avoid terms such as 'toss of a coin 'or 'decided by a computer' to explain randomisation. Instead explain that if the patient were to join the study, they would have an equal chance of having graded exercise therapy or activity management.
- Explain the rationale for randomisation (to avoid bias)
  - Cover the key points: we don't know the best treatment, we want a fair comparison between groups, the process of achieving this is randomisation to produce similar groups
    E.g. 'We don't know which way of treating patients with CFS/ME is best. We need to compare the two main treatments fairly. To do this we need similar groups of patients to have either activity management or graded exercise therapy. The only way to make sure that the groups of patients are as similar as possible is to have the allocation decided by a process called randomisation. If you agree to take part in the main study, you will have an equal chance of having graded exercise therapy or activity management. It is important that you only agree to take part if you are prepared to consider either treatment.'

University of BRISTOL

Recruitment Checklist	Discussed
Recording	
Background to study [*we need to know whether treatments are effective. This will help children in the future.]*	
What does being in the study involve?	
1. Explain the rationale for randomisation	
2. Questionnaires [*no detail, just that they will have them*]	
3. Accelerometer	
4. Discussion with a researcher (optional)	
Right to withdraw	
Data protection	
Explain the consent/assent forms	

Appendix 5 FITNET-NHS

[Reference: Baos, S., et al., Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to activity management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial. Trials, 2018. ***19****(1): p. 136.]*

FITNET-NHS: Inclusion/exclusion criteria

Inclusion criteria
1) Children aged 11 to 17 years 2) Children with CFS/ME (defined using NICE guidance*) 3) Children with no local specialist CFS/ME service *[*NICE: National Institute for Health and Clinical Excellence, Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) Diagnosis and management of CFS/ME in adults and children., N.I.f.H.a.C. Excellence., Editor. 2007, Developed by the National Collaborating Centre for Primary Care: London].*
Exclusion criteria
1) Children not disabled by fatigue 2) Children whose fatigue is due to another cause 3) Children or parents unable to complete video calls (e.g. Skype) or FITNET-NHS modules (e.g. unable to read FITNET-NHS material, or significant development problems, or limited internet access, unwilling/unable to set up personal email address/video call (e.g. Skype) account) 4) Children who report pregnancy at assessment

FITNET-NHS: Eligibility assessment

Young people without a local CFS/ME service were referred to the specialist paediatric CFS/ME service via their local primary care services. The eligibility assessment was carried out by a recruiter (health professionals from the specialist CFS/ME team) via telephone. Two telephone calls were made by the recruiter, an initial 10-minute call to establish whether the family were still interested in participating in the trial. If interested the family were then sent all relevant trial related documentation via email, including: PILs, consent to contact form and the Revised Children's Anxiety and Depression Scale questionnaire (RCADS*). After consent to contact and RCADS forms were returned, a decision was made in relation to trial eligibility. In addition to using RCADS scoring criteria, recruiters were able to seek additional guidance and clarification from a Clinical Psychologist if necessary when assessing for eligibility. After the assessment of eligibility was established, a second call was made by the recruiter to firstly screen for a diagnosis of CFS/ME using NICE guidelines and secondly complete a recruitment consultation if a young person was given a diagnosis of CFS/ME.

*[Reference: *Chorpita, B.F., C. Ebesutani, and S.H. Spence. Revised Children's Anxiety and Depression Scale questionnaire (RCADS). 2015. Available from: https://www.childfirst.ucla.edu/resources/.]*

FITNET-NHS: Revised Children's Anxiety and Depression Scale questionnaire

RCADS

Please complete the questionnaire below.

Thank you!

I agree for the data collected in this questionnaire to be stored as research data, which will be used if I later consent to take part in the study. I understand that this data may be used by clinicians providing my care. I understand that I can ask for this data to be deleted without it affecting my care.

◯ Yes
◯ No

RCADS
Please put a circle around the word that shows how often each of these things happen to you. There are no right or wrong answers.

Today's date: _____

	Never	Sometimes	Often	Always
1. I worry about things	◯	◯	◯	◯
2. I feel sad or empty	◯	◯	◯	◯
3. When I have a problem, I get a funny feeling in my stomach	◯	◯	◯	◯
4. I worry when I think I have done poorly at somthing	◯	◯	◯	◯
5. I would feel afraid of being on my own at home	◯	◯	◯	◯
6. Nothing is much fun anymore	◯	◯	◯	◯
7. I feel scared when I have to take a test	◯	◯	◯	◯
8. I feel worried when I think someone is angry with me	◯	◯	◯	◯
9. I worry about being away from my parents	◯	◯	◯	◯
10. I get bothered by bad or silly thoughts or pictures in my mind	◯	◯	◯	◯
11. I have trouble sleeping	◯	◯	◯	◯
12. I worry that I will do badly at my school work	◯	◯	◯	◯
13. I worry that something awful will happen to someone in my family	◯	◯	◯	◯

14. I suddenly feel as if I can't breathe when there is no reason for this	○	○	○	○
15. I have problems with my appetite	○	○	○	○
16. I have to keep checking that I have done things right (like the switch is off, or the door is locked)	○	○	○	○
17. I feel scared if I have to sleep on my own	○	○	○	○
18. I have trouble going to school in the mornings because I feel nervous or afraid	○	○	○	○
19. I have no energy for things	○	○	○	○
20. I worry I might look foolish	○	○	○	○
21. I am tired a lot	○	○	○	○
22. I worry that bad things will happen to me	○	○	○	○
23. I can't seem to get bad or silly thoughts out of my head	○	○	○	○
24. When I have a problem, my heart beats really fast	○	○	○	○
25. I cannot think clearly	○	○	○	○
26. I suddenly start to tremble or shake when there is no reason for this	○	○	○	○
27. I worry that something bad will happen to me	○	○	○	○
28. When I have a problem, I feel shaky	○	○	○	○
29. I feel worthless	○	○	○	○
30. I worry about making mistakes	○	○	○	○
31. I have to think of special thoughts (like numbers or words) to stop bad things from happening	○	○	○	○
32. I worry what other people think of me	○	○	○	○
33. I am afraid of being in crowded places (like shopping centers, the movies, buses, busy playgrounds)	○	○	○	○
34. All of a sudden I feel really scared for no reason at all	○	○	○	○

35. I worry about what is going to happen	○	○	○	○
36. I suddenly become dizzy or faint when there is no reason for this	○	○	○	○
37. I think about death	○	○	○	○
38. I feel afraid if I have to talk in front of my class	○	○	○	○
39. My heart suddenly starts to beat too quickly for no reason	○	○	○	○
40. I feel like I don't want to move	○	○	○	○
41. I worry that I will suddenly get a scared feeling when there is nothing to be afraid of	○	○	○	○
42. I have to do some things over and over again (like washing my hands, cleaning or putting things in a certain order)	○	○	○	○
43. I feel afraid that I will make a fool of myself in front of people	○	○	○	○
44. I have to do some things in just the right way to stop bad things from happening	○	○	○	○
45. I worry when I go to bed at night	○	○	○	○
46. I would feel scared if I had to stay away from home overnight	○	○	○	○
47. I feel restless	○	○	○	○

Baseline RCADS_v2.0, 21/09/2016

[Reference: Chorpita 2015, Revised Children's Anxiety and Depression Scale questionnaire (RCADS) Publisher: Child FIRST – Focus on Innovation and Redesign in Systems and Treatment. https://www.childfirst.ucla.edu/resources/]

FITNET-NHS: Integrated qualitative aims and objectives

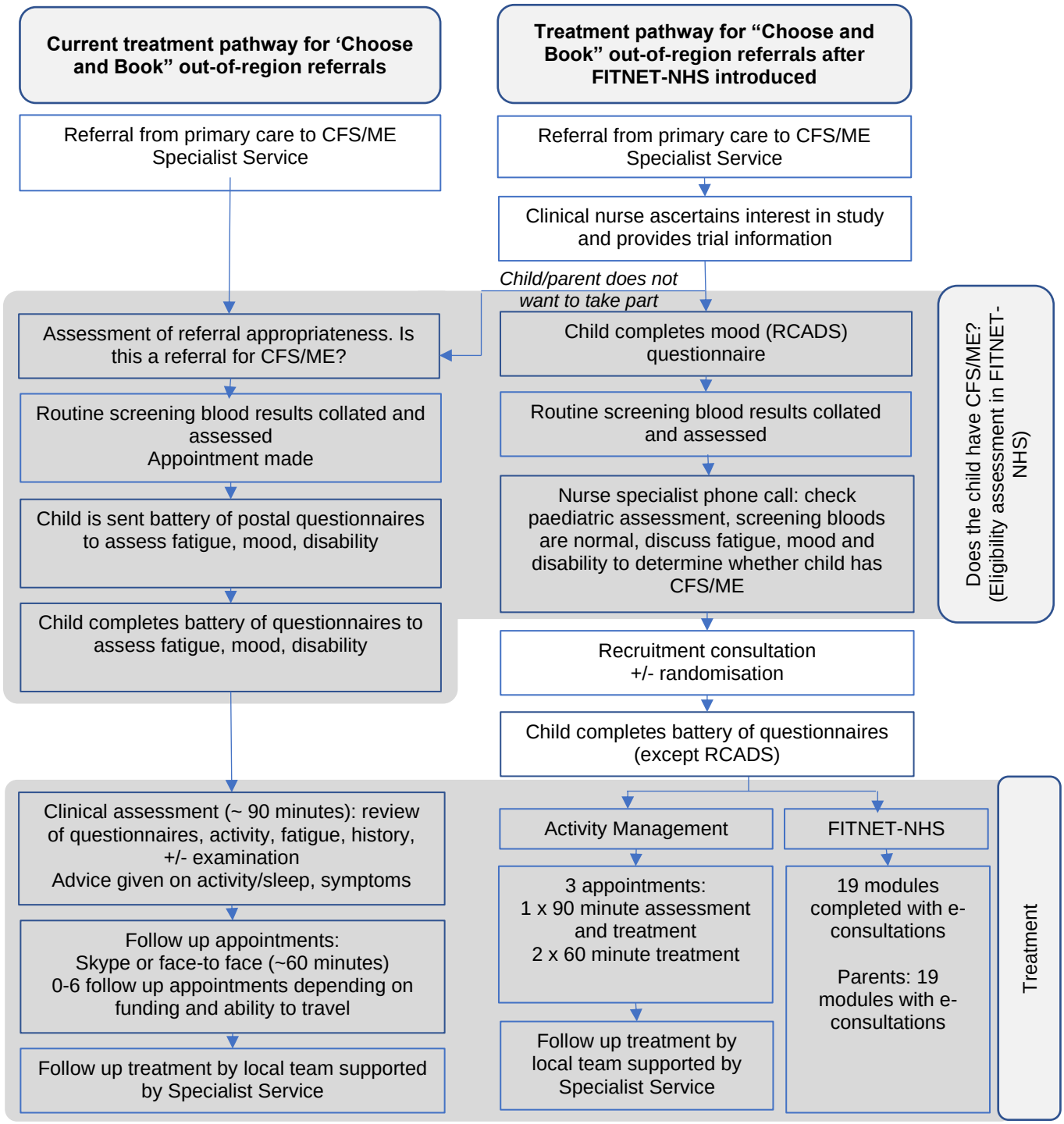
Integrated qualitative methodology was used to assess the feasibility and acceptability of conducting the FITNET-NHS RCT, specifically to understand issues that would relate to the successful design and implementation of a full-scale RCT in the UK, (the original FITNET trial* was conducted in the Netherlands). During the internal pilot phase qualitative methodology aimed to:

1. Examine whether it was feasible to recruit to FITNET-NHS (online delivery versus activity management (skype delivery) from a specialist service to patients in different regions of the UK.
2. Examine whether FITNET-NHS and activity management are acceptable interventions for children in different regions of the UK.

*[Reference: * Nijhof, S.L., et al., Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet, 2012. 379(9824): p. 1412-8.]*

FITNET-NHS: Trial flow

Participant flow through trial related interventions and data collection procedures.



FITNET-NHS: Data collection and randomisation

Randomisation and allocation outcome

The recruiter randomised those who provided assent/consent to participate. Randomisation was carried out via a web-based randomisation system, operated by the Bristol Randomised Trials Collaboration, (telephone randomisation was used on occasions when the web-based system was unavailable). Allocation to the two treatment groups of either FITNET-NHS (online CBT) or activity management via skype (allocation ratio 1:1). Minimisation was used to facilitate balance between treatment groups by age and gender. A random component was retained to prevent accurate prediction of allocation. Because of the nature of the intervention, it was not practical to blind either the family or the clinical service to treatment allocation.

FITNET-NHS: Intervention groups

FITNET-NHS Online CBT: Intervention Overview

(Protocol v1.0)

Participants first complete the psycho-educational components then work through 19 interactive modules over 6 months. Parent modules explore and address parent's beliefs and behaviours towards their child with CFS/ME focusing on their role as carers. The modules for participants introduce CBT, present CFS/ME as a multi-factorial model, discuss the role of the family and develop treatment goals. The CBT modules focus on cognitive behavioural strategies with instructions on exercises for identifying, challenging and changing cognitive processes. Modules 1, 2 and 4 introduce CBT and explain the role of therapists, present CFS/ME as a multifactorial model with predisposing, precipitating and maintaining factors and discuss the role of

the family. Modules 3 and 5 focus on treatment goals including the goal of full-time education. Modules 6 to 19 focus on cognitive behavioural strategies with instructions on exercises on identifying, challenging and changing cognitive processes that contribute to CFS/ME. Young people will be asked to do homework (answer questions and complete diaries). Whilst young people are able to complete the modules at their own pace, they will be encouraged to work on and complete modules before the next appointment.

After parents complete the psycho-educational sections, they separately complete 19 CBT modules. These explore and address parent's beliefs and behaviours towards their child with CFS/ME. In children younger than 15 years, parents are supported to act as a coach. In those older than 15, parents are encouraged to step back and support their child taking responsibility for their treatment. Parents complete diaries and questionnaires and there is a review function of all completed modules.

The FITNET-NHS clinical psychologists will make appointments and provide e-consultations. E-consultations are an email exchange between the therapist and the participants which functions only on the FITNET-NHS platform. In addition, participants and parents are required to complete homework (for example, sleep-wake, and thoughts and feelings diaries). These will be discussed in the e-consultations and used to support behaviour change. The therapist works with parents and young people separately and responding together is discouraged. Therapist and participants/parents arrange a convenient date and time for e-

consultations, usually every 2 weeks, unless the participant/parent and therapist feel the need for this to be different. Participants and parents will be asked to complete homework/tasks within specified time frames. Therapists will also respond to participants parents within the specified time frame. A chat function will be provided within working hours to answer simple questions.

Activity management via Skype: Intervention Overview

(Protocol v1.0)

Participants allocated to activity management will have up to three Skype appointments (one assessment and two follow-up). Parent/carer attendance is optional. Participants will then be discharged to their local service providers with up to 3 support phone calls. Activity management aims to convert a “boom-bust” pattern to a baseline with the same daily amount. For children/teenagers with CFS/ME these are almost entirely cognitive activities: school, schoolwork, reading, socialising, and screen time (phone, laptop, TV, games) but may also include some physical activities. Those allocated to this arm will receive advice about the total amount of daily activity, including physical activity, but will not receive specific advice about feelings, beliefs and behaviour change. Therapists treating children in both arms will be encouraged to offer routine advice about sleep, medication use and symptom control.

Young people, their parents/carers and the health professional providing the intervention will receive up to six activity management sessions over Skype and the

frequency of appointments (every 2-6 weeks). The baseline assessment should take around 90 minutes. The follow up assessment should take 60 minutes each. We will collect the number, frequency and duration of initial/follow up sessions for each participant. This data will be used in the FITNET-NHS cost-effectiveness analysis. Participants will not be able to cross-over to the other treatment arm.

Following the set of video calls the therapists will hand-over care to the local nominated health professional in primary/secondary care. Therapists will discuss the case by phone/letter (as normal clinical practice), ask for a review within six-eight weeks and offer up to three telephone calls to advise on treatment options, overcoming barriers and symptom control. The activity management Intervention Monitoring: Follow Up form can be used as a guide for the discussion with the local team and this can be stapled to the phone call discussion and placed in the medical notes. Local providers mostly offer face-to-face follow-up, some may use telephone.

Research team contact details:

Trial Manager: Email: Tel:

Activity Management Intervention Monitoring: Follow Up

Patient name: _____**Research ID:** __ __ __ __ __ __

Follow up session (circle)**: 1 2 3 4 5** or
Handover to local provider session (circle)**: 1 2 3**

Mandatory if not discussed	**Tick if discussed**	**Reason**
Has the participants managed the baseline for 1-2 weeks? Y / N		if yes:
Increase this baseline by 10-20% each week.		
Participants will continue to increase activity until they are able to do up to 8 hours of cognitive and physical activity a day.		
All participants:		
Discuss different types of activity, both cognitive and physical, which vary according to age.		
Discuss different types of cognitive activities (high and low concentration).		
Discuss physical activities, which vary according to severity (e.g. severely affected-sitting up in bed, mildly affected- running).		
Advise on **how** to record the total number of minutes spent each day doing high-energy activities using paper diaries/ “ActiveME” app or other methods. Discuss levels of activity and whether the baseline has been set at the correct level.		
Discuss problems and possible solutions, managing setbacks.		
Advice on sleep.		

Flexible (if applicable)	**Tick if discussed**	**Reason**
Advice on exercise: no. steps, mins. exercise, aerobic vs. non-aerobic activity, advice on exercises or using a strengthening programme (e.g. PE in school, attendance at sporting events, recording physical activity within total cognitive activity).		
Discuss anxiety and/or depression.		
Advice on medication (if required).		

Advice on symptom control (if required).		

Prohibited if discussed	**Tick if discussed**	**Reason**
Detailed discussion of feelings, beliefs and how they change.		
Diaries on feelings and their relationship with behaviour.		

Has an Adverse event been reported Y / N (if yes, please notify the research team and complete AE/SAE form)
Does patient need ActiveME App Y / N (if yes, please notify the research team)

Duration of session (circle appropriate)**:**
0 – 30 minutes **30 – 60 minutes** **60 – 90 minutes**

Name of assessor: _____
Today's date: __ __ **/** __ __ **/** __ __ __ __
(BLOCK CAPITALS)
Signature: _____

Date of next assessment: __ __ **/**__ __ **/** __ __ __ _ (~ 2-6 weeks after previous appointment)

FITNET-NHS: Information Leaflet for young people (11-15yrs) v1.0 18/08/2016

University of BRISTOL fitnetNHS Royal United Hospitals Bath NHS NHS Foundation Trust

How effective is FITNET-NHS for children and young adults with CFS/ME

Information Leaflet for Young People Aged 11-15 Years

We would like to invite you to take part in a research study which will tell us which of two treatments, FITNET-NHS and Activity Managements, is more effective at helping young people with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis.

Before you decide whether you would like to take part, it is important for you to understand *why* the study is being done and *what* it will involve. The leaflet is divided into two parts. Part 1 tells you about the study and what will happen to you if you choose to take part. Part 2 gives details about how the study will be run.

Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us.

Ask us if there is anything you don't understand or if you want more information.

Take time to decide whether or not you want to join in.

Thank you for reading this.

PART 1

Why are we doing the study?

We want to test whether a treatment called "FITNET-NHS", which delivers cognitive behavioural therapy (CBT) for CFS/ME at home via the internet, is effective and value for money. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. We want to compare this with another treatment for CFS/ME called Activity Management which will use video call (e.g. Skype).

In the first part of the study, we want to know whether young people, like you, will want take part in the study and whether young people think FITNET-NHS and Activity Management are acceptable treatments.

In the second part of the study, we want to see how effective FITNET-NHS and Activity Management are at treating young people with CFS/ME and measure the costs of each treatment.

Why have I been asked to take part?

You have been asked to take part in this study because you are aged between 11 and 17 years, have a diagnosis of CFS/ME, and do not have a specialist CFS/ME service close to your home.

If you are not able to attend telephone or online consultations required for the research study (e.g. you don't have a phone line or internet/video call (e.g. Skype) access at home), you will not be able to take part.

Do I have to take part?

You do not have to take part in this study. If you agree to speak to the research nurse, they will explain more about the study. This will not commit you to taking part.

If you think that you might not want to take part in any of the treatments, you should not enter the study.

We hope that up to 734 young people and their parents/carers will take part in this study but it is up to you to decide whether or not you would like to take part.

If I agree to take part can I change my mind?

Yes. If you decide you would like to take part but change your mind later, we will continue to follow you up like we do other young people who are not part of the study unless you tell us you don't want us to.

You can leave the study at any point and, if you would like us to, we will take out the information collected about you at any point before we carry out data analysis.

Leaving the study at any time will not affect the standard of medical care you will receive.

What will I be asked to do if I take part?

Before the treatment:

If you would like to hear more about the study, the research nurse will arrange a time to talk to you over the telephone. The research nurse will explain the study to you and your parents/carers, and answer any questions you may have. With your permission, this discussion will be audio-recorded and will last about 45 minutes, but you can talk for longer if you have more questions. The research nurse might ask you about how you felt when you were asked if you wanted to take part in this study.

If you want to take part in the study, you will be asked to fill in an on-line assent form to show us that you agree.

If you take part in this study, we need to make sure that participants in both groups are as similar as possible. This is the only way we can compare the groups and make sure the study is fair. You will therefore be allocated to either Activity Management or FITNET-NHS by a process of randomisation. Half of those taking part in the study will receive Activity Management and half will receive FITNET-NHS, so you will have a 50% chance of getting either treatment. Both treatments have been used before.

During the treatment:

You will receive treatment for your CFS/ME at home. **Both** groups will get lots of advice from members of Bath Specialist CFS/ME Service about how to improve your sleep and you will get treatment for your symptoms. You and your parents/carers will need to complete questionnaires at 3 months, 6 months and 12 months which will take you about 20 minutes each time.

We want to find out more about what you think about this study. A researcher may ask to meet with you or speak with you and your parents/carers over the phone to find out what you think about the study or the treatments. This discussion will be audio-recorded with your permission. This may last around 30 minutes. It is up to you if you want to do this or not.

In addition you will get either Activity Management or FITNET-NHS.

Activity Management

If you are in this group you will receive three video (e.g. Skype) calls. During the first video (e.g. Skype) call, you will have a detailed assessment of the activity you do. This includes thinking activity such as school work, homework, time on the computer and screens, reading and hobbies that require concentration and physical activity such as walking or PE. We call this high energy activity. We will ask you to record your activity on paper or our iPhone app "ActiveME". We will then help you find your "baseline" activity which is the average amount of activity that you can do each day. When you have found your baseline activity, we will provide follow up video (e.g. Skype) calls to help you increase this by 10-20% each week. This is called Activity Management.

FITNET-NHS

If you are in this group both you and your parents will have to work through 19 interactive cognitive behavioural therapy (CBT) treatment modules on-line. These modules will explain what CBT is and how it works. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. It also helps you develop treatment goals and discusses the role of your family in the treatment process. Your parents will also have to work through modules separately in which they will explore their beliefs and behaviours towards your CFS/ME and focus on their role as carers. The therapist will work with you and your parents and provide weekly online consultations to review homework and support you. With your permission we would like to save these electronic conversations.

What is the difference between the two treatments?

Activity Management will mainly be working on activities that take up most of the day like school work, setting a baseline and trying to increase it. It does not focus on changing behaviours and thought processes. FITNET-NHS will try to focus on cognitive behaviour strategies to change thought processes to allow you to reach a goal which you have set for yourself.

Are there any disadvantages to taking part in this study?

You will need to spend time talking to a research nurse for about 10 minutes so we can understand if you are interested in the study. You and your parents/carers will need to arrange a time to talk on the phone to a research nurse about the study. This will take about 45 minutes.

If you take part, you and your parents/carers will need to complete questionnaires at 3 months, 6 months and 12 months. We ask all young people to complete these questionnaires. These questionnaires will take you about 20 minutes each time.

You may not find the treatment you are offered helps you. Young people with CFS/ME can get worse even with the treatment offered and we do not know how many will get worse (or better) with either Activity Management or FITNET-NHS. This is why we are doing a study.

Will I experience any side effects from taking part in this study?

We have used Activity Management and face-to face CTB in our service and are not aware of any side effects. A study of on-line CTB treatment for children with CFS/ME has also shown that there were no side effects.

What are the benefits of taking part in this study?

You may feel better from the treatment you are undergoing, but we cannot say this for certain. You may learn something about how a research trial works. Some young people with CFS/ME like to know that they are helping others with CFS/ME in the future.

What will happen when the study stops?

After the study stops, you can continue to have medical care from your local team if you still need it. If you want to know the study results, let us know and we can send them to you.

PART 2

If you are still interested in taking part in this study, please read the information below before making your decision.

Consent

We have to be completely certain that you are happy to join this study, so we will ask you to sign an assent form. We will also ask you to sign one of these forms if you are happy for us to record discussions with you. Once you have signed the forms, you will still be free to stop the recording or leave the study at any point. Just tell us if this is the case. Whether or not you wish to take part, you will continue to receive the same care from the clinical team.

What will happen to the information you collect about me?

It is very important that all the information you give us is completely private. The conversations that you give us permission to record will be encrypted and password protected (so that only members of the study team can listen to them). They will be stored on a secure University of Bristol server.

We will use a research code to identify you. No name or personal information will be on the questionnaires we send you. All personal details that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS or University of Bristol computers.

We may use some of the things you say when we write about the study but we will take your name and any other information off so no one will know who was speaking.

We would also like to keep the things you say so that other researchers can use it for research and teaching now, and in the future. We will check you are happy for us to use the things you say in this way.

If you tell us something that makes us worried about your safety or the safety of those around you, we may have to discuss this with somebody else. This means, what you say would not be kept completely private if we were sufficiently concerned about you or those around you. We would do the same if you told us something in clinic.

What will happen if I feel unwell during the study?

If during the course of the study you start to feel unwell (e.g. if you feel anxious or depressed, or if you have a fever), you should speak to your parents and contact your local care providers (e.g. your GP or paediatrician). The research team provide specialist treatment for CFS/ME but cannot provide treatment for other problems you may have.

If you do contact the CFS/ME research team about other concerns (e.g. feeling anxious or depressed), the research team will do their best to help. If they feel it's appropriate they may pass the information on to your local care providers and try to inform you of other services which may help you. The CFS/ME research team may not be able to reply to your queries straight away (e.g. if you send the research team a message with concerns on a Saturday it may not be picked up until the Monday). This is why you should always speak to your parents and contact your GP if you have any concerns.

Does everybody involved in the study have the right police checks?

Yes. All those working in the study have had police checks to make sure they are safe to work with children and young people.

Who will know that I am taking part in the study?

Your GP should know that you are taking part in this study so we will write to them to tell them which treatment you will be receiving in the study.

What will happen to the results of the study?

This study will give us information on whether young people are interested in taking part in a study like this and whether they think the "Activity Management" and "FITNET-NHS" treatments are acceptable. It will also tell us how effective these treatments are at helping young people with CFS/ME and how much the treatments cost.

What if new information becomes available whilst I am in the study?

If new information becomes available, we will tell you about it and discuss whether you want to continue in the study.

Who is organising and funding the study?

This research is organised by Professor Esther Crawley who leads the Bath Specialist CFS/ME Service and the CFS/ME Research team at the University of Bristol.

The study is funded by the government's research fund - the National Institute of Health Research (NIHR) and is sponsored by the University of Bristol.

What should I do if I have a problem with the study?

If you have any problems with this study, please speak to your parents/carers, Professor (in place?) Esther Crawley, or any member of the clinical team that you know. Professor Crawley's contact information can be found at the end of this information leaflet.

You can also complain to the NHS in the usual way through the Patient Advice and Liaison Services (PALS) on 01225 473424.

Will I need to pay to be part of this study?

No.

Ethical Approval

Ethical approval means that this study is safe to carry out on young people. The study has been approved by <xxx>.

Who can I contact for further information?

- Paediatric Consultant/Clinical Lead of the Paediatric CFS/ME Service
  Address:
  Tel: *Email:*

Or if you want to talk to somebody independent please contact:

- Research Lead
  Address: RUH Bath NHS Foundation Trust, Combe Park, Bath, BA1 3NG
  Tel: *Email:*

THANK YOU for taking the time to read this leaflet

FITNET-NHS: Information Leaflet for young people (16-17yrs) v1.0 18/08/2016

University of BRISTOL fitnetNHS Royal United Hospitals Bath NHS NHS Foundation Trust

How effective is FITNET-NHS for children and young adults with CFS/ME

Information Leaflet for Young People Aged 16-17 Years

We would like to invite you to take part in a research study which will tell us how effective FITNET-NHS (online cognitive behavioural therapy) is compared to Activity Management for Chronic Fatigue Syndrome or Myalgic Encephalopathy (CFS/ME) in young people.

Before you decide whether you would like to take part, it is important for you to understand *why* the study is being done and *what* it will involve. The leaflet is divided into two parts. Part 1 tells you about the study and what will happen to you if you choose to take part. Part 2 gives details about how the study will be run.

Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us.

Ask us if there is anything you don't understand or if you want more information.

Take time to decide whether or not you want to join in.

Thank you for reading this.

PART 1

Why are we doing the study?

We want to test whether a treatment called "FITNET-NHS", which delivers cognitive behavioural therapy (CBT) for CFS/ME at home via the internet, is effective and value for money. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. We want to compare this with another treatment for CFS/ME called Activity Management which will be delivered via video call (e.g. Skype).

In the first part of the study, we want to know whether young people will take part in the study and whether young people, like you, think FITNET-NHS and Activity Management are acceptable treatments.

In the second part of the study, we want to see how effective FITNET-NHS and Activity Management are at treating young people with CFS/ME and measure the costs of each treatment.

Why have I been asked to take part?

You have been asked to take part in this study because you are aged between 11 and 17 years, have a diagnosis of CFS/ME, and do not have a local specialist CFS/ME service.

If you are not able to attend telephone or online consultations required for the research study (e.g. you don't have a phone line or internet/video call (e.g. Skype) access at home), you will not be able to take part.

Do I have to take part?

You do not have to take part in this study. If you agree to speak to the research team, they will explain more about the study. This will not commit you to taking part.

If you think that you might not want to take part in any of the treatments, you should not enter the study.

We hope that up to 734 young people and their parents/carers will take part in this study but it is up to you to decide whether or not you would like to take part.

If I agree to take part can I change my mind?

Yes. If you decide you would like to take part but change your mind later, we will continue to follow you up like we do other young people who are not part of the study unless you tell us you don't want us to.

You can leave the study at any point and if you would like us to, we will take out the information collected about you at any point before we carry out data analysis.

If you leave the study at any time, this will not affect the standard of medical care you will receive.

What will I be asked to do if I take part?

Before the treatment:

If you would like to hear more about the study, the research team will arrange a time to talk to you over the telephone. The research team will explain the study to you and your parents/carers, and answer any questions you may have. With your permission, this discussion will be audio-recorded and will last about 45 minutes, but you can talk for longer if you have more questions. The research team might ask you about how you felt when you were asked if you wanted to take part in this study.

If you want to take part in the study, you will be asked to fill in an on-line consent form to show us that you agree.

If you take part in this study, we need to make sure that participants in both groups areas similar as possible. This is the only way we can compare the groups and make sure the study is fair. You will therefore be allocated to either Activity Management or FITNET-NHS by a process of randomisation. Half of those taking part in the study will receive Activity Management and half will receive FITNET-NHS, so you will have a 50% chance of getting either treatment. Both treatments have been used before.

During the treatment:

You will receive treatment for your CFS/ME at home via the internet. **Both** groups will get lots of advice from members of Bath Specialist CFS/ME Service about how to improve your sleep and you will get treatment for your symptoms. You and your parents/carers will need to complete questionnaires at 3, 6 months and 12 months which will take you about 20 minutes each time.

We want to find out more about what you think about this study. A researcher may ask to speak with you and your parents/carers over the phone to find out what you think about the study or the treatments. This discussion will be audio-recorded with your permission. This may last around 30 minutes. It is up to you if you want to do this or not.

In addition you will get either Activity Management or FITNET-NHS.

Activity Management

If you are in this group you will receive three video (e.g. Skype) calls. During the first video (e.g. Skype) call, you will have a detailed assessment of the activity you do. This includes thinking activity such as school work, homework, time on the computer and screens, reading and hobbies that require concentration and physical activity such as walking or PE. We call this high energy activity. We will ask you to record your activity on paper or our iPhone app "ActiveME". We will then help you find your "baseline" activity which is the average amount of activity that you can do each day. When you have found your baseline activity, we will provide follow up video (e.g. Skype) calls to help you increase this by 10-20% each week. This is called Activity Management.

FITNET-NHS

If you are in this group both you and your parents will have to work through 19 interactive cognitive behavioural therapy (CBT) treatment modules on-line. These modules will explain what CBT is and how it works. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. It also helps you develop treatment goals and discusses the role of your family in the treatment process. Your parents will also have to work through modules separately in which they will explore their beliefs and behaviours towards your CFS/ME and focus on their role as carers. The therapist will work with you and your parents and provide weekly e-consultations to review homework and support you.

What is the difference between the two treatments?

Activity Management will mainly be working on activities that take up most of the day like school work, setting a baseline and trying to increase it. It does not focus on changing behaviours and thought processes. FITNET-NHS will try to focus on cognitive behaviour strategies to change thought processes to allow you to reach a goal which you have set for yourself.

Are there any disadvantages to taking part in this study?

You will initially need to spend time talking to the research team for about 10 minutes so we can understand if you are interested in hearing more about the study. If you are potentially interested in taking part, you and your parents/carers will need to arrange a time to talk on the phone to the research team to hear more about the study. This will take about 45 minutes.

If you take part, you and your parents/carers will need to complete questionnaires at 3, 6 months and 12 months. We ask all young people to complete these questionnaires. These questionnaires will take you about 20 minutes each time.

You may not find the treatment you are offered helps you. Young people with CFS/ME can get worse even with the treatment offered and we do not know how many will get worse (or better) with either Activity Management or FITNET-NHS. This is why we are doing a study.

Will I experience any side effects from taking part in this study?

We have used Activity Management and face-to face CTB in our service and are not aware of any side effects. A study of on-line CTB treatment for children with CFS/ME has also shown that there were no side effects.

What are the benefits of taking part in this study?

You may feel better from the treatment you are undergoing, but we cannot say this for certain. You may learn something about how a research trial works. Some young people with CFS/ME like to know that they are helping others with CFS/ME in the future.

What will happen when the study stops?

After the study stops, you can continue to have medical care from your local team if you still need it. If you want to know the study results, let us know and we can send them to you.

PART 2

If you are still interested in taking part in this study, please read the information below before making your decision.

Consent

We have to be certain that you are happy to join this study, so we will ask you to sign a consent form. We will also ask you to sign one of these forms if you are happy for us to record discussions with you. Once you have signed the forms, you will still be free to stop the recording or leave the study at any point. Just tell us know if this is the case. Whether or not you wish to take part, you will continue to receive the same care from the clinical team.

Will you access my health records?

A great deal of information is collected and stored about all of us in our official records. This information gives a detailed picture of many aspects of our life, such as our health and the treatment we get in the NHS. The FITNET-NHS study can use this together with the information you give us to help us understand how well FITNET-NHS works, how much the NHS spends on treatment and whether FITNET-NHS reduces or increases these costs. We will be able to tell whether those taking part in the study get other illnesses and check which treatments they get.

Information can only be released with your permission. In order to make sure we collect information on the right person we will provide the minimum necessary personal details (such as your name and address) to the organisations holding the information, for example your general practitioner (GP). These will only be used to identify your information. Before the organisations send any information you have authorised back to us, your name and other details will be removed. None of the information you have told us, will be given to these organisation. In the same way as the answers you give us in the questionnaires, the information from the sources will be kept completely confidential in accordance with the Data Protection Act. This process of bringing together all these different pieces of the jigsaw of our lives is called 'data-linkage'.

Health records include those held by your GP and The Health & Social Care Information Centre. This includes data on Hospital Episode Statistics (e.g. details of visits to your doctor and any treatment you were given; if you have ever been to hospital, why you were there and what happened whilst you were there) and the Mental Health and Learning Disabilities Data Set (e.g. details of treatment you may have received for things like depression and anxiety). When we ask for sensitive information it's because we want to use this information to help us understand why things are the way they are and use this understanding to help people to be healthier.

All you need to do is agree to us accessing your health records on the consent form and we will do the rest. We will regularly request copies of your records from the relevant organisations to look at additional information that may have been added.

You can chose not to agree to us accessing your medical records without it affecting your involvement in the rest of the study. You are free to tell us to stop at any time without giving a reason. Your decision will not in any way affect the treatment you get from the NHS.

What will happen to the information you collect about me?

Any information that you give us will be completely private. The conversations that you give us permission to record will be encrypted and password protected (so that only members of the study team can listen to them). They will be stored on a secure University of Bristol server.

We will use a research code to identify you. No name or personal information will be on the questionnaires we send you. All personal details that could identify you will be kept secure in locked cabinets in locked offices or password protected on secure NHS or University of Bristol computers.

We may use some of the things you say when we write about the study but we will take your name and any other information off so no one will know who was speaking.

We would also like to keep the things you say so that other researchers can use it anonymously for research and teaching now, and in the future. We will check you are happy for us to use the things you say in this way.

If you tell us something that makes us worried about your safety or the safety of those around you, we may have to discuss this with somebody else. This means, what you say would not be kept completely private if we were sufficiently concerned about you or those around you. We would do the same if you told us something in clinic.

What will happen if I feel unwell during the study?

If during the course of the study you start to feel unwell (e.g. if you feel anxious or depressed, or if you have a fever), you should contact your local care providers (e.g. your GP or paediatrician). The research team provide specialist treatment for CFS/ME but cannot provide treatment for other problems you may have.

If you do contact the CFS/ME research team about other concerns (e.g. feeling anxious or depressed), the research team will do their best to help. If they feel it's appropriate they may pass the information on to your local care providers and try to inform you of other services which may help you. The CFS/ME research team may not be able to reply to your queries immediately (e.g. if you send the research team a message with concerns on a Saturday it may not be picked up until the Monday). This is why you should always contact your local care provider if you have any health-related concerns.

Does everybody involved in the study have the right police checks?

Yes. All those working in the study have had police checks to make sure they are safe to work with children and young people.

Who will know that I am taking part in the study?

Your GP should know that you are taking part in this study so we will write to them to tell them which treatment you will be receiving in the study.

What will happen to the results of the study?

This study will give us information on whether young people are interested in taking part in a study like this and whether they think the "Activity Management" and "FITNET-NHS" treatments are acceptable. It will also tell us how effective these treatments are compared with each other at helping young people with CFS/ME and how much the treatments cost.

What if new information becomes available whilst I am in the study?

If new information becomes available, we will tell you about it and discuss whether you want to continue in the study.

Who is organising and funding the study?

This research is organised by Professor Esther Crawley who leads the Bath Specialist CFS/ME Service and the CFS/ME Research team at the University of Bristol.

The study is funded by the government's research fund - the National Institute of Health Research (NIHR) and is sponsored by the University of Bristol.

What should I do if I have a problem with the study?

If you have any problems with this study, please speak to your parents/carers, Professor (in place?) Esther Crawley, or any member of the clinical team that you know. Professor Crawley's contact information can be found at the end of this information leaflet.

You can also complain to the NHS in the usual way through the Patient Advice and Liaison Services (PALS) on 01225 473424.

Will I need to pay to be part of this study?

No.

Ethical Approval

Ethical approval means that this study is safe to carry out on young people. The study has been approved by <xxx>.

Who can I contact for further information?

Prof Esther Crawley - Paediatric Consultant/Clinical Lead of the Paediatric CFS/ME Service

Address: /

Tel: *Email:*

Or if you want to talk to somebody independent please contact:

Tel *Email:*

THANK YOU for taking the time to read this leaflet

FITNET-NHS: Information leaflet for parents

v1.0 18/08/2016

University of BRISTOL fitnetNHS Royal United Hospitals Bath NHS Foundation Trust

How effective is FITNET-NHS for children and young adults with CFS/ME

Information Leaflet for Parents/Carers

We would like to invite your child to take part in a research study which will us how effective FITNET-NHS (online cognitive behavioural therapy) is compared to Activity Management for Chronic Fatigue Syndrome or Myalgic Encephalopathy (CFS/ME) in young people.

Before you decide whether you would like your child to take part, it is important for you and your child to understand *why* the study is being done and *what* it will involve. The leaflet is divided into two parts. Part 1 tells you about the study and what will happen to your child if you choose for them to take part. Part 2 gives details about how the study will be run.

Please read this leaflet carefully. You can talk about it with your family, friends, doctor, or us.

Ask us if there is anything you don't understand or if you want more information.

Take time to decide whether or not you want to join in.

Thank you for reading this.

PART 1

Why are we doing the study?

We want to test whether a treatment called "FITNET-NHS", which delivers cognitive behavioural therapy (CBT) for CFS/ME at home via the internet, is effective and value for money. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. We want to compare this with another treatment for CFS/ME called Activity Management which will be delivered via video call (e.g. Skype).

In the first part of the study, we want to know whether young people will take part in the study and whether young people think FITNET-NHS and Activity Management are acceptable treatments.

In the second part of the study, we want to see how effective FITNET-NHS and Activity Management are at treating young people with CFS/ME and measure the costs of each treatment.

Why has my child been asked to take part?

Your child has been asked to take part in this study because they are aged between 11 and 17 years, have a diagnosis of CFS/ME and do not have a local specialist CFS/ME service.

If you feel that either you or your child will not able to read and understand the study materials or have no phone or internet/video call (e.g. Skype) access this would mean they should not take part.

Does my child have to take part and can I change my mind?

Your child does not have to take part in this study. If you and your child agree to speak to the research nurse who will explain more about the study, this will not commit your child to taking part in the study.
If you would not want your child to take part or receive one of the treatments in this study, you should not allow your child to enter the study.
If you decide you would like your child to take part but change your mind later, we will continue to follow your child up like we do other young people who are not part of the study unless you tell us you don't want us to. You can withdraw your child from the study at any point.

We hope that up to 734 young people and their parents/carers will take part in this study but it is up to you to decide whether or not you would like your child to take part. If you decide you would not like you child to take part or decide to withdraw your child at any time, this will not affect the standard of medical care your child will receive.

What would we ask you and your child to do?

Before the treatment:

If you would like further information about the study, the research team will arrange a time to discuss the study with you and your child over the telephone. The research team will explain the study and answer any questions you may have. This discussion will be audio-recorded with your permission and will last about 45 minutes but you can talk for longer if you have more questions. The research team may ask you and your child about how you felt when you were asked if you wanted to take part in this study.

If you and your child agree to take part in the study, you will be asked to fill in an on-line consent form to confirm this.
If your child takes part in the study, we need to make sure that both groups are as similar as possible. This is the only way we can compare groups and make sure the study is fair. You child will be allocated to either Activity Management or FITNET-NHS by a process of randomisation (in other words, by chance). Half of those taking part in the study will receive Activity Management and half will receive FITNET-NHS, so your child will have a 50% chance of getting either treatment. As this study is trying to compare both treatments it will not be possible for you to choose which treatment you would like for your child. Both treatments have been used before.

During the treatment:

Your child will receive treatment for their CFS/ME at home via the internet. Children in **both** groups will receive an assessment, treatment and advice from members of Bath Specialist CFS/ME Service about how to improve symptoms and sleep. You and your child will need to complete questionnaires at 3, 6 months and 12 months which will take you about 20 minutes each time.

We want to find out more about what you and your child think about this study. A researcher may ask to speak with you and/or your child over the phone to find out what you think about the study or the treatments. With your permission we would like to audio-record these discussions. This may last around 30 minutes. It is up to you and your child if you want to do this or not.

In addition, your child will get either Activity Management or FITNET-NHS.

Activity Management

If your child is in this group they will receive three video (e.g. Skype) calls. During the first video (e.g. Skype) call, they will have a detailed assessment of the total activity they do each day. This includes thinking activity such as school work, homework, time on the computer and screens, reading and hobbies that require concentration and physical activity such as walking or PE. We call this high energy activity. We will ask them to record their activity on paper or our iPhone app “ActiveME”. We will then help them find their “baseline” activity which is the average amount of activity that they can do each day. When they have found their baseline activity, we will provide follow up video (e.g. Skype) calls to help them increase this by 10-20% each week. This is called Activity Management.

FITNET-NHS

If your child is in this group both you and they will have to work through 19 interactive cognitive behavioural therapy (CBT) treatment modules on-line. These modules will explain what CBT is and how it works. CBT focuses on cognitive behavioural strategies to identify, challenge and change cognitive (thinking) processes. It also helps you develop treatment goals and discusses the role of your family in the treatment process. Parent's modules explore and address parent's beliefs and behaviours towards their child with CFS/ME focussing on their role as carers. The therapist works with parents and children separately and provide weekly e-consultations with children and parents to review homework and support behaviour change.

What is the difference between the two treatments?

Activity Management will work on the total amount of activity done each day, by setting a baseline and trying to increase it over time. FITNET-NHS will try to focus on cognitive behaviour strategies to change cognitive processes which will allow a child to reach a goal which they have set themselves.

Are there any disadvantages to my child taking part in this study?

You and your child will initially need to spend time talking to the research team for about 10 minutes so we can understand if you are interested in hearing more about the study. If you and your child are potentially interested in taking part, you and your child will need to arrange a time to talk on the phone to the research team to hear more about the study. This will take about 45 minutes.

If you take part, both you and your child will need to complete questionnaires at 3, 6 months and 12 months after starting the study. We ask all children to complete these questionnaires. We will also ask you to complete questionnaires so we can measure the cost of treatment. These questionnaires will take you about 20 minutes each time.

Treatments for CFS/ME don't help everybody and you may find the treatment your child has been offered does not help them. This could be true for both treatments. Young people with CFS/ME can get worse with any intervention offered and we do not know how likely this is.

Will my child experience any side effects from taking part in this study?

We have used Activity Management and face-to face CTB in our service and are not aware of any side effects. A study of on-line CTB treatment for children with CFS/ME has also shown that there were no side effects.

What are the benefits of my child taking part in this study?

Your child may benefit from the treatment they receive, but we cannot guarantee this. Some children with CFS/ME like to know that they are helping other children in the future. Your child may also learn about research.

What will happen when the study stops?

After the study stops, your child can continue to have medical care from their local team if they still need it. Research can take quite a long time but if you give us your email address we will write to you and let you know what we find out when we finish the study if you are interested.

PART 2

If you are considering your child taking part in this study, please read the additional information below before deciding.

Consent

We have to be certain that you and your child are happy to join in this study, so if you say you are, we will ask you to sign our consent form. We will also discuss the study with your child and ask them to sign an assent form if they are aged between 11 -15 or a consent form if they are aged between 16 –17. We will also ask you and your child to sign one of these forms if you are happy for us to record discussions with you. Even if you do sign the forms on behalf of your child, you will be free to stop the recording or withdraw your child at any point. Just tell us if this is the case. Whether or not you wish your child to participate, your child will continue to receive the same care from the clinical team.

Will you access my child's health records?

A great deal of information is collected and stored about all of us in our official records. This information gives a detailed picture of many aspects of our life, such as our health and the treatment we get in the NHS. The FITNET-NHS study can use this together with the information you and your child give us to help us understand how well FITNET-NHS works, how much the NHS spends on treatment and whether FITNET-NHS reduces or increases these costs. We will be able to tell whether those taking part in the study get other illnesses and check which treatments they get.

Information can only be released with your/your child's permission. In order to make sure we collect information on the right person we will provide the minimum necessary personal details (such as your name and address) to the organisations holding the information, for example your general practitioner (GP). These will only be used to identify your information. Before the organisations send any information you have authorised back to us, your name and other details will be removed. None of the information you have told us, will be given to these organisations. In the same way as the answers you give us in the questionnaires, the information from the sources will be kept completely confidential in accordance with the Data Protection Act. This process of bringing together all these different pieces of the jigsaw of our lives is called 'data-linkage'.

Health records include those held by your GP and The Health & Social Care Information Centre. This includes data on Hospital Episode Statistics (e.g. details of visits to your doctor and any treatment you were given; if you have ever been to hospital, why you were there and what happened whilst you were there) and the Mental Health and Learning Disabilities Data Set (e.g. details of treatment you may have received for things like depression and anxiety). When we ask for sensitive information it's because we want to use this information to help us understand why things are the way they are and use this understanding to help people to be healthier.

If your child is aged between 11-15 years of age, all you need to do is agree to us accessing your child's health records on the consent form and we will do the rest. If your child is 16-17 years of age we will ask them whether they are happy for us to access their health records. We will regularly request copies of your child's records from the relevant organisations to look at additional information that may have been added.

You can chose not to agree to us accessing your child's medical records without it affecting your child's involvement in the rest of the study. You are free to tell us to stop at any time without giving a reason. Your decision will not in any way affect the treatment your child gets from the NHS.

Your privacy and data protection

Any information that you give us will be completely private. The conversations that you have given your permission to be recorded will be encrypted and password protected (so that only members of the study team can listen to them). They will then be stored on a secure University of Bristol server.

We will use a research code to identify your child's data. No name or personal information will be on the questionnaires we send out to you or your child. All personal details that could identify you or your child will be kept secure in locked cabinets in locked offices or password protected on secure NHS or University of Bristol computers.

Quotes from conversations will be used when results are published but the names of the people quoted will not be used so no one will know who was speaking. We would like to keep anonymised data and quotes collected during the study so that the University of Bristol's School of Social and Community Medicine can use it for research and teaching purposes now, and in the future. We will ask you to tell us if you are happy for us to them in this way.

If you or your child tell us something that makes us worried about yours or your child's safety, we may have to discuss this with somebody else as we need to be sure you and your child are safe. This means, what you say would not be kept completely private if we are sufficiently concerned about you or those around you. We would do the same if you told us something in clinic.

What will happen if my child feels unwell during the study?

If during the course of the study your child starts to feel unwell (e.g. if they feel anxious or depressed, or if they have a fever), you should contact your child's local care providers (e.g. GP or paediatrician). The research team provide specialist treatment for CFS/ME but cannot provide treatment for other problems your child may have.

If your child does contact the CFS/ME research team about other concerns (e.g. feeling anxious or depressed), the research team will do their best to help. If they feel it's appropriate they may pass the information on to your child's local care providers and try to inform your child of other services which may help. The CFS/ME research team may not be able to reply to your child's queries immediately (e.g. if your child sends the research team a message with concerns on a Saturday it may not be picked up until the Monday). This is why you should always contact your local care provider if you or your child have any health-related concerns.

Does everybody involved in the study have the right police checks?

Yes. All those working in the study have had the necessary police checks to make sure they are safe to work with children and young people.

Who will know that my child is taking part in the study?

Your child's GP should know that they are taking part in this study so we will write to them to tell them which treatment your child will be receiving in the study.

What will happen to the results of the study?

This study will give us information on whether young people are interested in taking part in a study like this and whether they think the "Activity Management" and "FITNET-NHS" treatments are acceptable. It will also tell us how effective these treatments are at helping young people with CFS/ME and how much the treatments cost.

What if new information becomes available?

If new information becomes available, we will tell you and your child about it and discuss with you and your child whether you want to continue in the study.

Who is organising and funding the study?

This research is organised by Professor Esther Crawley who leads the Bath Specialist CFS/ME Service and the CFS/ME Research team at the University of Bristol.

The study is funded by the government's research fund - the National Institute of Health Research (NIHR) and is sponsored by the University of Bristol.

What should I do if I have a problem with the study?

If you have any problems with this study, please speak to Professor Esther Crawley or any member of the clinical team. Professor Crawley's contact details can be found at the end of this leaflet.

In the event that something does go wrong and your child is harmed during the research and this is due to someone being careless then you may be able to take legal action to get repayment from the hospital but in this case you may need to pay a lawyer to help you. You can also use the normal National Health Service system for complaints: Patient Advice and Liaison services (PALS) 01225 473424.

Will I need to pay for my child to be part of this study?

No.

Ethical Approval

Ethical approval means that this study is safe to carry out on young people. The study has been approved by <xxx>.

Contact details and further information

- Paediatric Consultant/Clinical Lead of the Paediatric CFS/ME Service
  Address:
  Tel: *Email:*

Or if you want to talk to somebody independent please contact:

- Research Lead
  Address:
  Tel: *Email:*

THANK YOU for taking the time to read this leaflet

FITNET-NHS: Interview Topic Guide Young People

v0.2 09/02/2017

Introduction

☐ **Introduce research:** We want to talk to families who are taking part in the trial about: their experience so far, the information they were given and how they are finding the treatment. What families tell us is used to understand if the treatment is acceptable and improve the trial.

☐ **Procedures:** Usually done over Skype or the telephone. Chat to child and parent separately or together if they prefer, 20-40 mins- can stop when you want to, audio record, everything will be anonymised.

☐ **Separate from treatment**

☐ **Questions, happy?**

☐ **Sign Consent Forms (REDCap)** (Child Assent (12-15), Consent (16-18), Parent Consent for Child (12-18), Parent Consent)

Demographics (Child)

Male ☐ Female ☐

Age: _____

School attendance: _____

Diagnosis/ length of illness: _____

_____

Trial Arm: ☐ FITNET ☐ Activity Management

How far through treatment (FITNET modules (/19)/ Skype calls (/3): _____

_____

Interview Date:_____

Interviewed: ☐ Skype ☐ Telephone ☐ Home

Child & Parent: ☐ Together ☐ Separately

Interview

1. **Can you tell me a bit about your chronic fatigue?**
   Prompts: Impact on your life? Journey before the specialist service? Previous treatment/ management to help it- what worked/ didn't work?

Provision and acceptability of patient information & recruitment process:

2. **How did you hear about the study?**
   Prompts: What did you think when you were told about it? What kinds of things did you like about it? What kind of things were you/they worried about?

3. **What did you think about the information you were given about the study?**
   Prompts: PIS?- read it?, understand it?, enough information/too much? Things missing? Seek information elsewhere (what)? How did you find the phone calls with the research team?- things missing, did not understand?

4. **What were you told about the treatments?**
   Prompts: Both FITNET & AM- what did you think? What did you already know (from where)? Did you understand? Understand what was going to happen next? Feelings?

5. **What were the most important messages told to you by the research team?**
   Prompts: Treatment plan? Benefits/risks? Recordings? Recovery?

6. **What did you think about having treatments allocated by randomisation, i.e. by chance?**
   Prompts: How do you feel about this way of deciding your treatment? Happy? Did you wonder why this is done? Did you think you were likely to get one treatment rather than the other? Is there a better way? Why?

7. **Did you discuss the study with anyone else e.g. your/their GP?**
   Prompts: Local CFS/ME specialist? Are you getting any advice about your/their CFS/ME from anyone else? E.g. Online? Other sources of information?

Reasons for accepting participation:

8. **What did you think when you were told you got [FITNET-NHS/AM]?**

Prompts: How did you feel? Was it what you expected/wanted? Favoured a treatment? What would you have done if allocated the other treatment? Worries?

9. **What did you think about when deciding whether or not to take part in the study?**
   Prompts: Treatments offered? Randomisation? What did you already know? Favoured a particular treatment? Helping other people or not? Worries?

Acceptability of FITNET-NHS:

10. **What were your first thoughts about following an online treatment programme?**
    Prompts: Did you think it would work? Any worries?

11. **Tell me about the FITNET treatment you are/were receiving?**
    Prompts: What you expected? What has happened? What is good/bad about it? Would you change anything about it (what)? How are you/they doing (is it working)?

12. **How are you getting on with the FITNET-NHS online chapters?**
    Prompts: How do you find using it? Is it age appropriate? Any technical problems? Any benefits? Worries? What do you think about modules? How do you feel about the frequency of the e-consultations? How do you feel about the advice you get? How do you feel about the homework you are asked to do? Do the modules make you feel more or less anxious, or about the same?

13. **Are there any things we need to consider for people your age when using it?**
    Prompts: Text, Chapters? E-consultations? Homework? Advice?

Acceptability of the AM Skype Calls:

14. **What were your initial thoughts about speaking to a doctor/ being treated using Skype?**
    Prompts: Did you think it would work? Any worries?

15. **Tell me about the AM you are/were receiving?**
    Prompts: What you expected? What has happened? What is good/bad about it? Would you change anything about it (what)? How are you/they doing (is it working)?

16. **How are you getting on with the video (e.g. Skype) calls?**

    Prompts: How do you find using it? Is it age appropriate? Any technical problems? Any benefits? Worries? Prompts: What do you think about video

(e.g. Skype) calls? How do you feel about the frequency of the video calls? How do you feel about the advice you get? How do you feel about the homework you are asked to do?

17. **Are there any things we need to consider for people your age when using it?**
    Prompts: Calls? Assessments? Advice?

And finally:

18. **What do you think now about being involved in the FITNET-NHS study?**
    Prompts: Would you do it again? Would you recommend it to a friend of they had CFS/ME? What do you think about the study for others your age?

19. **Is there anything else you would like to tell me?**
    Prompts: About the study? Things we need to improve/ change? Taking part in research in general? Are there any questions you would like to ask?

FITNET-NHS: Interview Topic Guide Parents/Carers

v0.2 09/02/2017

Introduction

☐ **Introduce research:** We want to talk to families who are taking part in the trial about: their experience so far, the information they were given and how they are finding the treatment. What families tell us is used to improve the trial.

☐ **Procedures:** Usually done over Skype. Chat to child and parent separately, short-20 mins- can continue if you want to, audio record, everything will be anonymised, stop at any time.

☐ **Separate from treatment**

☐ **Questions, happy?**

☐ **Sign Consent Forms (REDCap)** (Child Assent (12-15), Consent (16-18), Parent Consent for Child (12-18), Parent Consent)

Demographics (Child)

Male ☐ Female ☐

Age: _____

Ethnicity: _____

School attendance: _____

Diagnosis/ length of illness: _____

_____

Hometown: _____

Trial Arm: ☐ FITNET ☐ Activity Management

How far through treatment (FITNET modules/ Skype calls): _____

_____

Interview Date:_____

Interviewed: ☐ Skype ☐ Home Child & Parent: ☐ Together ☐ Separately

Interview

1. **What led to [child] being referred to the CFS/ME specialist service?**
   Prompts: Did CFS/ME have an impact on your child's life? If so, did you/they do anything to manage it in any way or not? What things were you doing to help it before you started to see the specialist service?

2. **Can you talk me through [child's] initial appointment with the specialist service?**
   Prompts: What was said, did you understand what was being said? Feelings?

Provision and acceptability of patient information & recruitment process:

3. **What were your initial thoughts about the research study?**
   Prompts: What did you think when you were told about it? What kinds of things did you like about it? What kind of things were you/they worried about?

4. **What did you think about the information you were given about the study?**
   Prompts: What information did you get – verbal and written (PIS)? Did you read it? Understand it? Did it give you enough information/too much? Were there things you thought they had forgotten to include? Did you supplement this information with that from other sources or not? If so, what information/which sources?

5. **What did the research team tell you about the treatments?**
   Prompts: What did they say? What did you already know? When/Where did you find this out? What did you think? Depending on which treatment they talk about first: What did [they] mention about the other [FITNET-NHS/AM] treatment? Did you understand what was being said? What did you think? Did you understand what was going to happen next? Feelings?

6. **What were the most important messages conveyed to you during the discussion with [name - the research nurse] about the research study?**
   Prompts: Treatment plan? Benefits/risks? Recordings? Recovery?

7. **What did you think about having treatments allocated by randomisation, i.e. by chance?**
   Prompts: How do you feel about this way of deciding what treatment you get? Were you happy to be randomised? Did you wonder why this is done? Did you think you were likely to get one treatment rather than the other? Is there a better way? Why?

8. **Did you discuss the study with anyone else e.g. your/their GP?**
   Prompts: Local CFS/ME specialist? Are you getting any advice about your/their CFS/ME from anyone else? E.g. Online? Other sources of information?

Reasons for accepting participation:

9. **What did you think about when deciding whether or not to take part in the study?**
   Prompts: Treatments offered? Randomisation? What did you already know? Favoured a particular treatment? Did you think about the study in terms of helping other people or not? [Altruism? EC interested] *only if chose to take part and not mentioned yet.* Worries?

10. **What did you think when you were told your child got [FITNET-NHS/AM]?**
    Prompts: How did you feel? Was it what you expected/wanted? What do you think about the treatments [FITNET-NHS/AM] offered in this study? Why did you decide [not] to accept the [treatment] allocated to [name] at randomisation? What would you have done if allocated the other treatment? Favoured a particular treatment? What did you already know? Randomisation? Expectations? Worries? Issues over participation? Engagement?

Acceptability of FITNET-NHS/AM:

11. **Do you think the FITNET-NHS/AM had an effect on you/your child or not?**
    Prompts: Their CFS/ME, themselves, how you/they manage their CFS/ME? School? Life in general?

12. **Tell me about the [FITNET-NHS/AM] you are/were receiving?**
    Prompts: What has happened? What is good/bad about it? Would you change anything about it? If so what? Structure of sessions? How was it explained to you? What did you expect it to be like? Is it age appropriate? How are you/they doing? What are you/they doing? What kind of things have you/they been worried about? How do you feel after a follow up session/module completion?

Acceptability of the FITNET-NHS online modules:

13. **What were your initial thoughts about following an online treatment programme?**
    Prompts: How do you find using it? Is it age appropriate? Any technical problems? Any benefits? Worries?

14. **How are you getting on with the FITNET-NHS online modules?**
    Prompts: What do you think about modules? How do you feel about the frequency of the e-consultations? How do you feel about the advice you get? How do you feel about the homework you are asked to do? Do the modules make you feel more or less anxious, or about the same?

15. **Are there any things we need to consider for children your child age or parents when using it?**
    Prompts: Modules? E-consultations? Homework? Advice?

Acceptability of the AM Skype Calls:

16. **What were your initial thoughts about your child speaking to a doctor/ being treated using Skype?**
    Prompts: How do you find using it? Were you on the call? Is it age appropriate? Any technical problems? Any benefits? Worries?

17. **How are you getting on with the video (e.g. Skype) calls?**

    Prompts: What do you think about video (e.g. Skype) calls? How do you feel about the frequency of the video calls? How do you feel about the advice given? How do you feel about the homework? Do the modules make you feel more or less anxious, or about the same?

18. **Are there any things we need to consider for people your child's age when using it?**
    Prompts: Calls? Assessments? Advice?

And finally:

19. **What do you think now about being involved in the FITNET-NHS study?**
    Prompts: Would you do it again? Would you recommend it to a friend of they had CFS/ME? What do you think about the study for other families?

20. **Is there anything else you would like to tell me?**
    Prompts: About the study? Randomisation? Taking part in research in general? Are there any questions you would like to ask?

FITNET-NHS Recruitment training methods

Members of a clinical CFS/ME team were responsible for eligibility screening and conducted all recruitment consultations during the FITNET-NHS RCT. Rates of recruitment were also monitored on a monthly basis during the FITNET-NHS trial, as they had been during the MAGENTA RCT (see: The impact of communication training on recruitment figures).

The 'MAGENTA: Tips for Recruitment and informed consent' document was adapted to support FITNET-NHS recruiters (FITNET-NHS: Tips for Recruitment and informed consent). All FITNET-NHS recruiters had previously recruited to paediatric RCTs (including MAGENTA). An initial face-to-face group training session (lasting approximately 1.5 hours) was led by two qualitative researchers, (by LB & RP) in month three of the FITNET-NHS trial. Training drew upon analyses of recruitment consultations conducted in the first three months of the trial.

Relevant sections of recruitment consultations were routinely recorded and analysed by the FITNET-NHS qualitative researcher (RP) on an ongoing basis, as had been the case in the MAGENTA RCT. Samples of recruitment consultations were also listened to in full and analysed by LB and NM, these consultations were discussed with RP to develop ongoing tailored group training. Follow-up training was conducted at the beginning of months six, nine and 12 (each 1 hour in duration). Examples from previous months recruitment consultations were used to highlight good practice, and areas where changes could be made to improve communication about the RCT. Written feedback was provided for recruiters, (by LB & RP) should they wish to refer to it at a later date. The FITNET-NHS 'tips for recruitment' document was developed further in month six of the trial to incorporate findings from analyses of recruitment

consultations. Further information was added highlighting similarities between the two intervention arms, (e.g. sleep advice was provide in both intervention arms) to emphasise that both were active treatments, and that both arms offered treatment tailored to the individual:

FITNET-NHS: Tips for Recruitment and informed consent

v1.0 29/11/2016

University of BRISTOL

fitnetNHS

Royal United Hospitals Bath NHS

USER GUIDE 05

A randomised controlled trial of Fatigue In Teenagers on the interNET (FITNET) compared to Activity Management (AM) to treat paediatric CFS/ME

FITNET-NHS: Tips for Recruitment and informed consent

Please consider these suggestions along with your own individual style.

Recording

- Please **audio-record** all discussions with patients, providing they are happy for you to do so. This gives us an insight into what works so we can help you and others to recruit effectively.
- Please read out the patient **'Consent ID'** and the **date** at the beginning of each recording.

Discussing the study:

- Be mindful to convey equipoise throughout
- Ask patients to 'keep an open mind' until all information is heard
- Avoid the term 'trial' and use the term 'study'
- Present the study in an enthusiastic and straight-forward manner
- **Establish Uncertainty:**
  e.g. 'We don't know which treatment is best for children/young people with CFS/ME. Because we don't know which is best, we're doing a study called FITNET-NHS'
- **Explain the benefits of study participation:**
  e.g., 'In the first phase of the study we will try to find out if patients would like to take part and whether they find the treatments acceptable. In the second phase we will compare the two treatments so that future patients will not have to face the current treatment uncertainties'

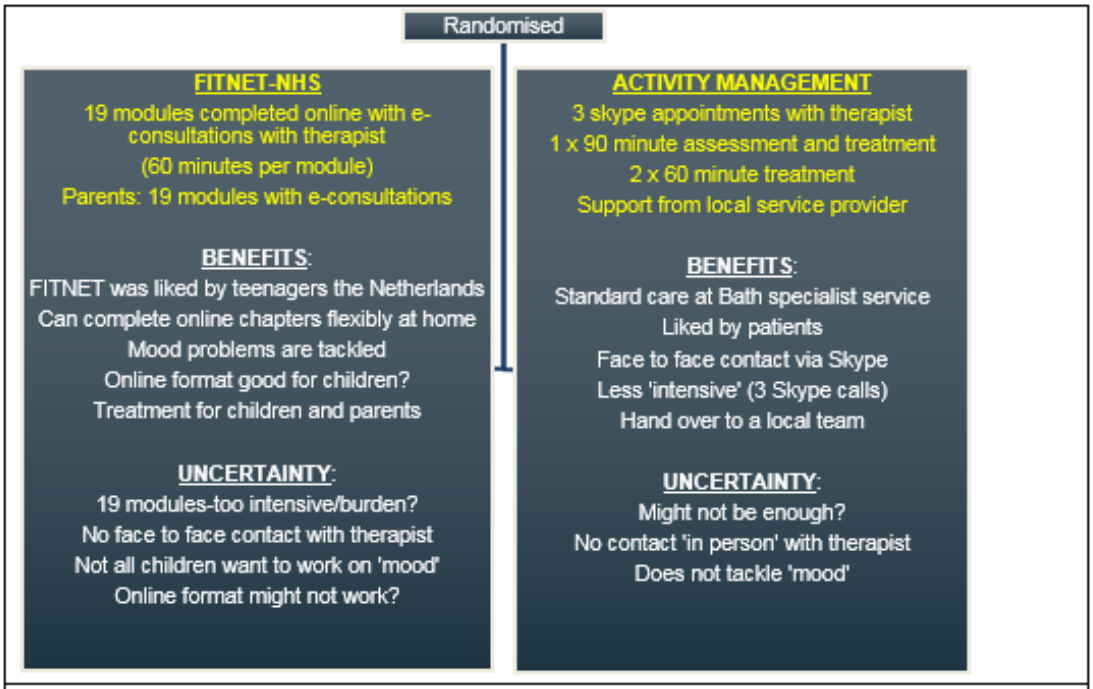
Discussing the procedures:

- **Provide an outline of each treatment**
  Emphasise that activity management and CBT are currently used in our specialist service, delivered *face to face.*
  e.g. 'At Bath, both activity management and CBT are good and standard approaches for the treatment of CFS/ME, but we don't know if FITNET-NHS is better/worse than AM by skype
  the Dutch study was comparing FITNET with no treatment'
- **Present balanced information about both treatments:**
  - Spend equal time discussing the benefits and uncertainty of each treatment
  - Avoid loaded terminology= e.g. *'gold standard', 'experimental', 'the first/second treatment'*

Preference Discussion:

In the SMILE trial, parents were more likely to express their preferences during the recruitment discussion. It's important to give children the opportunity to express their views about both treatments during this discussion, before randomisation.

- **Elicit and address patients' concerns/preferences:**
  An indirect, open question early on will elicit concerns or preferences
  e.g. '*What were your thoughts when you first heard about the study/treatments?'*
- Gently find out the reasons why a patient prefers/is concerned about one option over the other. This will enable you to correct any misunderstandings and ensure they understand both treatments well enough to make an informed decision. Tailor information to the patient and/or parent individual concerns.
- Remind the patient at the end of the discussion that regardless of which treatment they are allocated to, they will be treated with the best possible care and the health professional treating them will be experienced in that technique.



Randomisation:

- It is best to avoid terms such as 'toss of a coin 'or 'decided by a computer' to explain randomisation. Instead explain that if the patient were to join the study, they would have an equal chance of having skype activity management or online CBT.
- **Explain the rationale for randomisation (to avoid bias):**
  Cover the key points: we don't know the best treatment, we want a fair comparison between groups, the process of achieving this is randomisation to produce similar groups

  e.g. 'We don't know which way of treating patients with CFS/ME is best. We need to compare the two main treatments fairly. To do this we need similar groups of patients to have either skype activity management or online CBT. The only way to make sure that the groups of patients are as similar as possible is to have the allocation decided by a process called randomisation. If you agree to take part in the main study, you will have an equal chance of having activity management or CBT. It is important that you only agree to take part if you are prepared to consider either treatment.'

What does being in the study involve?

1. Skype calls with activity management or an online platform and e-consultations with FITNET-NHS
2. Questionnaires at baseline, 3, 6 and 12 months (children and parents)
   [*no detail, just that they will have them*]
3. Discussion (interview) with a researcher about their experiences (optional)

Right to withdraw at any time

Data protection (name will not appear)

Explain the consent/assent forms

Appendix 6 CONTRACT

[Reference: Hutchings, N., et al., CONTRACT Study - CONservative TReatment of Appendicitis in Children (feasibility): study protocol for a randomised controlled Trial. Trials, 2018. 19(1): p. 153.]

CONTRACT: Inclusion/exclusion criteria

Inclusion/exclusion criteria
Inclusion Criteria 1. Child age 4 – 15 years (<16 years and >3 years) 2. Clinical diagnosis, either with or without radiological assessment, of acute appendicitis which prior to study commencement would be treated with appendicectomy 3. Written informed parental consent, with child assent if appropriate Exclusion Criteria 1. Clinical signs or radiological findings to suggest perforated appendicitis 2. Presentation with appendix mass 3. Previous episode of appendicitis or appendix mass treated non-operatively 4. Major anaesthetic risk precluding allocation to the appendicectomy arm 5. Known antibiotic allergy preventing allocation to non-operative treatment arm 6. Antibiotic treatment started at referring institution (defined as 2 or more doses administered) 7. Cystic fibrosis (there is a higher background incidence of appendicitis in this population and they are at an increased risk of recurrence. Therefore, there is a lack of equipoise between treatment arms for this group of children) *8.* Positive pregnancy test *9.* Current treatment for malignancy

CONTRACT: Eligibility assessment

Eligible participants were identified by surgeons when diagnosed with acute appendicitis. The trial was explained to parents and young people via recruitment consultations conducted by surgeons and supported by research nurses. Age appropriate information sheets and a short video presentation were available to support the verbal discussion (recruitment consultation) of the trial provided by surgeons. Consent for trial participation was obtained from parents within four hours of first discussing the trial. Young people aged 12-years or older were asked to provide assent if they felt well enough to do so. At this time, written consent was also obtained for use of the audio-recorded recruitment consultation for research purposes.

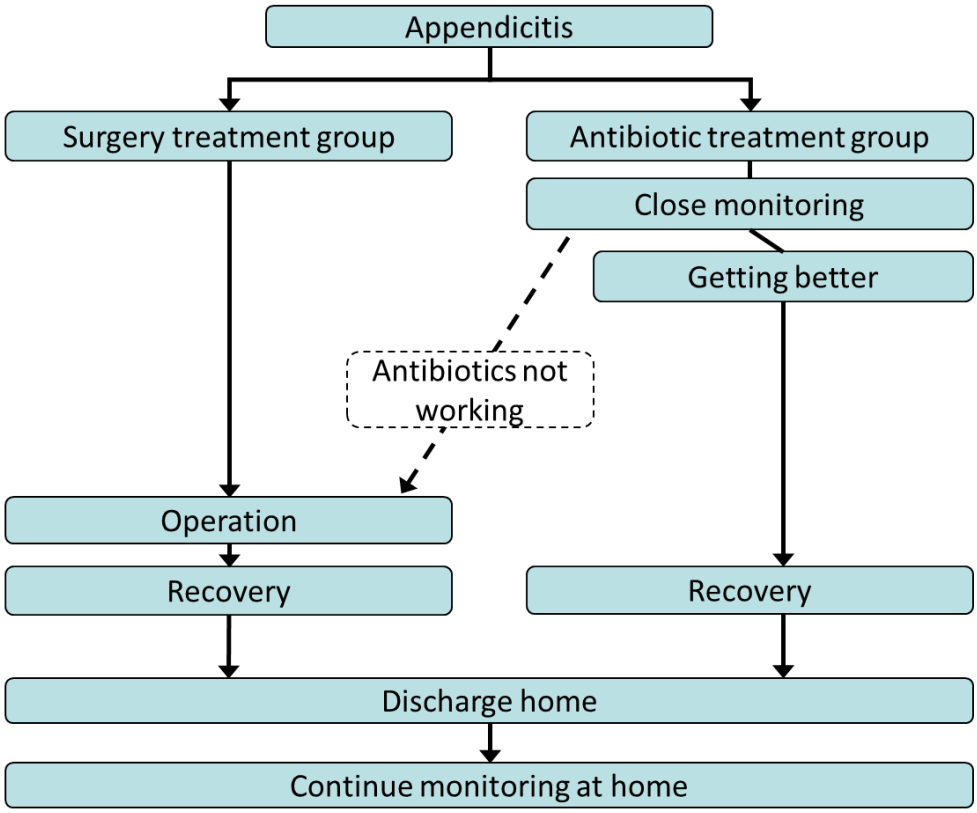
CONTRACT: Integrated qualitative aims and objectives

Integrated qualitative methodology was a key element in the CONTRACT feasibility trial and was used to assess the feasibility and acceptability of conducting a future trial. The CONTRACT Communication Sub-Study (CCSS) aimed to:

1. Monitor and optimise recruitment and informed consent during the feasibility stage of trial, to inform the design and conduct of a future trial.
2. Investigate the acceptability to families of the recruitment consultation, trial interventions and wider trial processes.
3. To identify potential barriers to recruitment and improve informed consent.

CONTRACT Trial flow

From the CONTRACT parent information leaflet version 2.1:



From the CONTRACT Health Technology Application: Submitted 17/09/15:

Antibiotics not working

Children receiving non-operative treatment who, in the opinion of the consultant surgeon in charge of their care have clinically deteriorated such that immediate appendicectomy is mandated, will undergo appendicectomy at any stage. A formal review will be performed at 24 hours following randomisation and any child deemed to have significantly deteriorated will undergo appendicectomy. Those who are stable or clinically improving will continue with non-operative treatment. Those who are not showing clinical signs of improvement at 48 hours following randomisation will undergo appendicectomy. These decision points will be made based on the clinical judgement of the treating consultant as is current practice rather than on any predefined set of criteria for which evidence does not currently exist. Children who require appendicectomy for failure of non-operative treatment will be treated post-operatively according to a standardised treatment regime already in use at our institutions and identical to that to be used in children in the appendicectomy treatment group.

CONTRACT: Data collection and randomisation

Recording of recruitment to trial consultations

Surgeons and research nurses sought verbal permission to record recruitment consultations with all families of young people eligible for the trial. A digital recorder and instructions on use were available at each participating site (D, E and F). Health professionals were advised to store the digital recorder in an accessible but secure location. Recruitment consultations were conducted in accident and emergency departments and inpatient wards at participating sites. Recruitment consultations included information in relation to the CONTRACT trial, and interventions, potential risks and benefits of taking part and answered any questions raised by the families.

Randomisation and allocation outcome

The CONTRACT protocol stated that informed consent and randomisation to the trial should happen within four hours of the initial trial consultation. After randomisation, the appropriate treatment pathway was administered immediately. Allocation to the two treatment groups of either antibiotics or surgery, (allocation ratio 1:1) used minimisation to ensure similarity between the groups in factors associated with diagnostic accuracy and outcome of treatment. Randomisation was carried out via an online system available 24-hours per day with telephone back-up provided by the relevant Clinical Trials Unit. Because of the nature of the interventions, it was not practical to blind either the family or the clinical service to treatment allocation. Families were given their randomisation outcome immediately and the appropriate treatment pathway was administered immediately.

CONTRACT: Intervention groups

Non-operative intervention (antibiotics)

Non-operative participants were monitored regularly and remained nil by mouth for a minimum 12-hour period. When participants had been afebrile for 24-hours they changed to oral antibiotics. Criteria for discharged home was based on: vital signs within normal limits for age, afebrile for >24 hours, tolerating light diet orally, mobilising and adequate oral pain relief. Participants received a total course of 10 days of antibiotics following randomisation. Parents were provided with information about the risk of recurrence and what to do should they feel they require further advice about their child's condition from the clinical team. The definition of recurrent acute appendicitis was based on histopathological evidence of acute appendicitis following readmission during the 6-month follow-up period. Readmitted participants were recorded and treated at the discretion of the clinical team to whom they present. These participants were not eligible for re-enrolment in the study.

Operative intervention (appendectomy)

A peritoneal microbiology swab was taken from each participant and sent for microbiological culture. Standardised treatment pathways at participating institutions were used to determine the duration of post-operative antibiotic regimes. These were based on histopathological evidence obtained from the removed organ, participants with a macroscopically normal appendix or simple acute appendicitis received no further antibiotics. Participants with a gangrenous or perforated appendix continued to receive intravenous antibiotics for a minimum of 3-5 days, (intravenous and oral). Criteria for discharge home was identical to those in the non-operative treatment group. Readmitted participants (due to surgical complications or infection) were recorded and treated by the clinical team to whom they presented.

CONTRACT: Information Leaflet for young people (8-11yrs) v2.0 11/01/2017

[Trust headed paper]

CONTRACT

University Hospital Southampton NHS
NHS Foundation Trust

CONservative TReatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

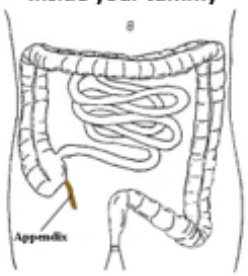
INFORMATION SHEET FOR YOUNG PEOPLE (8-11 yrs)

We want to ask for your help in a project that we are doing. This piece of paper explains a bit about the project. If there is anything that you want to know or do not understand please ask us or your parents.

Why are we doing this project?

You have come into hospital with tummy pain and your doctors think you have an illness called appendicitis. It means that a small part of your insides called the appendix became red and swollen and started hurting. Your appendix is of no use to you at all!

Inside your tummy



Our project is to try to find out the best way to treat children like you. Usually children with appendicitis get an operation to take the appendix away. We are trying to find out if an operation is really always needed or if children like you could be treated with medicines instead, called antibiotics.

In our project some children will have an operation and some will just have the antibiotics. We hope this will tell us which way is best way of treating children like you.

What will happen to me if I do take part?

If you agree to help us with our project, we will ask a computer program to decide whether you have an operation to take away your appendix or whether we give you the antibiotics. This process is called randomisation. You will have an equal chance of having either treatment, and using a computer program is the fairest way to decide which treatment you should have.

Whichever treatment you have, you will need to be in hospital for a few days. You will have some medicine through a drip in your hand or arm (a very small and

usually painless plastic tube) as well as some medicine to take the pain away. We will keep a close eye on you to make sure you are getting better and once you are well enough we will let you go home. It will take a little while for you to get completely better, but it won't be long before you should be doing all the things you usually do.

What are the risks?

All treatments that doctors do carry a small number of risks. The risks of having an operation are that there is a small chance of developing a problem after the surgery which we would have to treat. We may also find that you didn't actually have appendicitis in which case you would have had an operation that you didn't need.

The main risk of being treated with antibiotics is that they don't make you better as well or as quickly as we hope. This is very unlikely and because we will be keeping a close eye on you we will know about this. If this is the case we will need to do the operation to make you better. The other risk is that you may get appendicitis again. The risk of this is about 1 in 7 children. If you are unlucky and this happens then we will definitely do the operation to remove your appendix. This is the reason we would like you to come back to visit us after you have been in hospital – so we can make sure you are doing OK.

Will taking part help me?

Taking part in this project will not actually help you physically, but we need to treat your appendicitis anyway. We hope this project will help children like you in the future, by learning how best to treat appendicitis. After we have finished the study we can let you know the results if you would like to know.

Do I have to take part?

No, it is up to you and your parents. If you decide not to take part no one will be upset or disappointed.

Who will know that I am taking part in the study?

We will only tell those people who need to know including your family doctor.

Thank you for reading this sheet. Please ask if you have any questions.

A copy of this sheet should be given to the child and a copy placed in the child's medical record.

CONTRACT: Information Leaflet for teenagers (12-15yrs) v2.0 11/01/2017

[Trust headed paper]

CONTRACT

University Hospital Southampton NHS
NHS Foundation Trust

CONservative TReatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

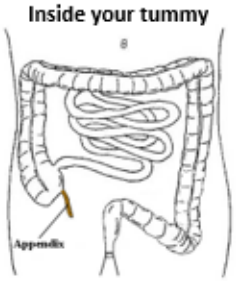
INFORMATION SHEET FOR TEENAGERS (12-15 yrs)

We are asking you to take part in a research project. Before you decide we want to explain to you a bit about the project and what it will mean for you. You should talk to you parents about it. If there is anything that you want to know or do not understand please ask us.

Why are we doing this research?

You have come into hospital with stomach pain and your doctors think you have an illness called appendicitis. Your appendix is a little tube attached to your large intestine that has no function at all! It doesn't usually cause any problems, unless it becomes infected, when it becomes red and sore. This is called appendicitis.

Inside your tummy



We are doing a project to learn about how *best* to treat children with appendicitis. Up to this point, all children needed an operation to remove the appendix. Although the operation works very well, we *now* know that it's also possible to treat appendicitis just with medicines called antibiotics. It could be better and easier for children and their families if an operation was not necessary.

So, in this project we want to find out whether the usual operation, or giving kids antibiotics, works better to get rid of appendicitis.

To do this, in the project some children will have an operation and some will just have the antibiotics. By comparing these treatments we hope to be able to tell if children really need surgery for appendicitis or if they can be treated just as well with antibiotics

What will happen to me if I do take part?

If you and your parents agree to be in our project, we will ask a special computer program to decide which treatment you will have, a process that is called 'randomisation'. One treatment will be the operation, one treatment will be antibiotics. It's important to have the computer program do this for us, so that everyone has the same chance of either having the antibiotics, or having the operation. You will only have one treatment, and **even if you don't want to take part in this study, we will still need to treat you for your appendicitis.**

If you have **an operation** this takes about an hour and is done whilst you are asleep. You will have one or more small cuts on your stomach and need to be in hospital for a day or 2 afterwards. You'll probably have some pain in your stomach and not be able to run around or be as active as you usually are for a while after the operation, even after you go home.

If you have **antibiotics** then these will be given through a drip. This is a small and usually painless tube in your hand or arm. We will ask you not to eat or drink for about 12 hours. You will need to spend at least 24 hours in hospital. Once you are getting better we will give you antibiotic medicine by mouth, and send you home. You will need to carry on taking the medicine for just over a week.

No matter which treatment you receive (operation or antibiotics), we will keep a very close eye on how you are doing to make sure that you are getting better. You will need to stay in hospital for a

bit and have some medicines through a drip. We will give you pain killers to help decrease your pain.

Once you have got better and gone home we will ask you to come back several times in the first 6 months so we can check up on you.

As an extra part of the project we will also ask you and your parents if we can record the conversation when we talk to you about the project. This is so we can find out what people think of the study and improve it in the future. We may also ask if it is OK to visit you at home in a few weeks time to ask you what you thought of the project.

Do I have to take part?
No, taking part is up to you and your parents. If you do decide to take part then you will be asked to sign a form to say you agree to take part. You can keep this sheet to read. You can ask questions about this study at any time.

If you decide at any time not to go ahead with all the things that are involved in the study, you can ask us to stop. (So, for example, if you decide after you leave the hospital that you don't want us to check in with you anymore, that's perfectly OK.)

If you decide not to take part in the study whatsoever, you do not have to give a reason and no one will be upset or disappointed. Don't worry, whatever you decide about taking part in this project, we'll still treat you for your appendicitis and take very good care of you.

What are the risks?
All treatments that doctors do carry a small number of risks. The risks of having an operation are that there is a small chance of developing a problem after the operation, which we would have to treat (such as an infection). We may also find that you don't actually have appendicitis in which case you would have had an operation that you didn't need.

The main risk of being treated with antibiotics is that they don't make you better as quickly as we hope. This is very unlikely and because we will be keeping a close eye on you we will know about this. If this is the case we will have to go ahead with the usual operation to remove your appendix. The other risk is that you may get appendicitis again. The risk of this is low (about 1 in 7 children). If you are unlucky and this happens then we will definitely do the operation to remove your appendix. This is the reason we would like you to come back to visit us after you have been in hospital – so we can make sure you are doing OK.

Will taking part help me?
Taking part will not actually help you physically because we'll treat your appendicitis anyway, but we hope that it will help children like you in the future. Some children like taking part in studies because they find it interesting to learn more about research, and to help other children. After we have finished the project we can let you know the results if you are interested.

Who will know that I am taking part in the study?
We will only tell those people who need to know including your family doctor.

How to contact the researchers
If during the course of the project you have any questions, please feel free to contact your doctor or nurse. These details can be found on your Parent's Information sheet

A copy of this sheet should be given to the child and a copy placed in the child's medical record.

CONTRACT: Information leaflet for parents

v4.10 9/11/2017

[Trust headed paper]

CONTRACT

University Hospital Southampton NHS
NHS Foundation Trust

CONservative TREatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

PARENTS INFORMATION SHEET

We are asking you and your child to take part in a research project. Before you decide it is important that you understand why the research is being done and what it will mean for you and your child. You should discuss this with your doctor. Please ask us if there is anything else that is not clear or you would like to know.

Why do we do research in healthcare?
Research is really important so that we can improve how we treat patients. If no research took place then it would be difficult to improve outcomes for patients. All research in the NHS is voluntary.

Why are we doing this research?
Your child has been diagnosed with acute appendicitis which means inflammation of the appendix. The standard treatment of acute appendicitis is an operation to remove the inflamed appendix. Parents often ask if children with appendicitis can be treated without an operation. Recently some studies have shown most children with appendicitis can be treated with antibiotics instead of an operation. But no studies in children have compared the advantages and disadvantages of having antibiotic treatment instead of surgery. The purpose of our study is to see if children with acute appendicitis can be treated equally effectively with antibiotics as with an operation. The study will also show if there are extra benefits of having antibiotics instead of surgery.

What will happen to my child if we do take part?
If you agree to take part in the study we will use a computer to decide at random whether your child will have their appendicitis treated with just antibiotics or with an operation. The chance of treating with either antibiotics or surgery is equal. Even if you don't consent to your child taking part in this study, we will still treat your child for their appendicitis.

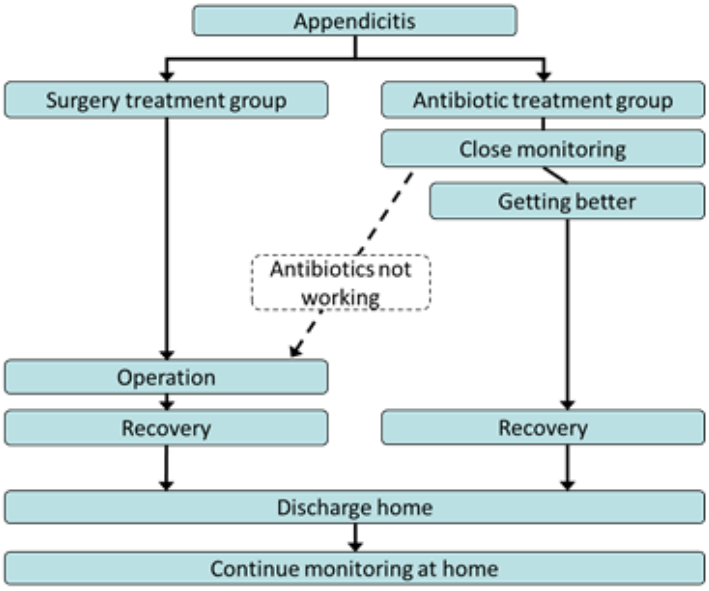
Operation Group: If your child is treated with surgery, he/she will have an operation to remove the inflamed appendix. This will require general anaesthesia and one or more small scars on the tummy. **The timing of surgery will be determined by how unwell your child is and how many other emergency operations need to be performed in the hospital.** Your child will be monitored by nurses and doctors before and during the operation, and afterwards on the ward. Once your child is stable, able to take fluid, food and painkillers by mouth, and move around, he/she will be allowed home.

Antibiotic Treatment Group: If your child is treated with antibiotics, he/she will receive antibiotics through a drip and not take any food or fluid for a minimum of 12 hours. Your child will be monitored on the ward by nurses and doctors. Once we are happy that your child is improving we will change to antibiotics by mouth. When it is clear your child is getting better, able to take fluid, food and painkillers by mouth, and move around your child will be allowed home. Your child will need to continue taking antibiotics by mouth for about a week.

Children in both groups will be monitored closely during their time in hospital to make sure they are getting better. When you go home you will be given information about who to contact if you are concerned about your child's recovery. You will be seen in the outpatient clinic at 6 weeks (as is current routine care). For the purposes of this research project we will ask you to visit us again in the clinic or contact you by telephone

after 3 months and 6 months. At these visits and during the stay in hospital we will ask you to fill in a short questionnaire about your child's health status. We will give you an extra questionnaire at discharge to fill in and return 2 weeks after you have gone home. With your permission we will also keep your contact details for a maximum of 5 years as we may wish to contact you to check on your child's progress in the future.

The figure below gives an overview of how the study works



What are the risks and benefits?
It is important that you and your child understand the risks and benefits of each of these options.

An operation: Having an operation will require general anaesthesia and involves a small number of risks related to surgery including bleeding, wound infection, a collection of pus in the abdomen, and in rare cases bowel obstruction requiring further surgery. There is also a 10% chance that the operation may show a healthy appendix, which means that the surgery was not necessary. In this case we will remove the appendix anyway. The benefit of an operation is that we know that surgery is an effective treatment for appendicitis.

Antibiotics: If your child is treated with antibiotics, there is a small risk that antibiotic treatment may not work. However, data we have collected on children such as yours who have been treated with antibiotics suggest that it works in the majority of cases (97%). We will monitor your child closely whilst he/she is in hospital and if there is no improvement by 48 hours with antibiotic treatment, he/she will be referred for an operation to remove the appendix. The precise timing of surgery will be determined by how unwell your child is and how many other emergency operations need to be performed in the hospital. The other risk of antibiotic treatment is that your child will still have his/her appendix and may get appendicitis again. If this were to happen then we would remove the appendix. Based on the research that has been done so far, we believe the risk of this is low (about 14% or 1 in 7

children in the first year). The potential benefit of antibiotic treatment is that your child may avoid an operation and general anaesthesia altogether.

What are the potential benefits of taking part?
This study will not bring any immediate benefit to your child. We hope that we will get information about how best to treat children such as yours in the future. After we have finished the study we can let you know the results if you would like. We do hope that the information gained from this study will be beneficial to children with appendicitis and their families in the future. By participating, you will be helping us to learn whether treatment with antibiotics is as good as surgery so that we may be able to offer this routinely as a treatment for other children in the future.

CONTRACT Communication study
In addition to the main study comparing antibiotics and surgery, we would also like to talk to people about their feelings about this study so that we can improve the ways that we communicate with families about studies like this in the future. It is important for us to talk to people who agree to take part in the main study as well as those who decide not to. With your permission we would like to record the conversation you have with the doctor and nurse about this study. We may also ask if a researcher from the Communication Study can contact you in a few weeks time to talk to you about your experience of being involved in the study. Again we will ask you for your permission to record this conversation.

Who is funding the research?
This project is funded by the National Institute for Health Research, which is the research arm of the NHS.

Will we be paid for being part of the study?
You and your child will not be paid to participate in the study. However we will reimburse your expenses for each of the additional follow-up appointments you attend at 3 and 6 months after going home (maximum £10 per visit).

Where is the study taking place and who is running it?
The study is being run by a group of surgeons at 3 specialist centres in the UK. Initially we are doing a small study in these 3 hospitals to figure out if this research is feasible. If it is feasible, we want to extend this to a much larger study. We also have a group of researchers interested in what influences children and families to take part in research studies. A group of parents and children are also helping to make sure the study is as child and family friendly as possible. For instance they have helped us write this information sheet.

The overall research study is being sponsored by University Hospital Southampton NHS Foundation Trust and is being co-ordinated by the Southampton Clinical Trials Unit.

Do I have to take part?
No, taking part is up to you and your child. If you decide not to take part you do not have to give a reason and your child's treatment will not be affected in any way. Your child will receive the standard treatment which your child's doctors will discuss with you. If you choose to let your child take part in this study you can take your child out of the study at any time.

How long do I have to decide?
Because we would like to start treating your child soon we will need to know if you are willing to take part within the next four hours. To help you decide please talk about the project to your research nurse and doctor. Please ask them any questions you may have.

If you agree to take part we will ask you to sign a consent form which indicates your agreement to take part in the research project and to let the researchers look at your child's health records. We will put a copy of this research consent form in your child's patient health records. We will give you a copy for your files.

Who will know that I am taking part in the study?
All the information we keep about your child and all conversations we record will be kept confidential. This means that we will only tell those people who need to know. This will include members of the research team for the purposes of contacting you during the study. With your permission we will let your child's GP know that he/she is taking part in this study. A copy of your child's consent form will also be sent to the Southampton Clinical Trials Unit who manage the study, to confirm you are happy for your child to take part.

Employees of the sponsor of the study, or the regulator of the study may need to see your child's health record to check on the study – this is a routine process of research in the NHS.

Availability of Research Results
The results of the study are likely to be published in medical journals. You and your child's name will not be identified in any report or publication. If you would like, we will also send a summary of the results of the study to you and your family doctor or paediatrician.

What are the arrangements for compensation?
All research in the NHS is looked at by a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the South Central – Hampshire A Research Ethics Committee.

If taking part in this research study harms your child, there are no special compensation arrangements. If your child is harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay legal costs. Regardless of this, if you wish to complain, or have concerns about any aspect of the way you or your child have been approached or treated during the course of this study, the normal National Health Service complaints mechanism will be available to you.

If you have private medical insurance, you may wish to check with your company before agreeing to take part in the study to ensure that participation in the study will not affect your insurance cover.

Details on how to contact the researchers:
If during the course of the study, you have any questions regarding your child's participation or would like study specific information, please contact.

Local Principal Investigator
Name of local PI
Local PI contact details (email and phone)

Chief Investigator for the overall study
Mr Nigel Hall
Consultant Paediatric Surgeon
Southampton Children's Hospital
n.j.hall@soton.ac.uk

In case of complaint please contact the Patient Support Services for advice:

Address, phone and email of local PALS service

Thank you for taking the time to read this information sheet

A copy of this sheet should be given to the parents and a copy placed in the child's medical record.

CONTRACT: Interview Topic Guide parents/carers

v8.0 05/12/2017

CONTRACT Communication Sub-Study – Possible questions for parents/carers.

The list of questions below are just indications of the sorts of topics we plan to explore. We will always tailor questions for each person depending on their situation (e.g. whether the family participated in CONTRACT or not) and what is important for them as an individual.

As we interview more people over the course of the study and learn what questions are the most important to ask, we will usually refine or change questions.

Setting the scene

1. **What led to [child's name] being brought in to hospital?**

Prompts: Symptoms? Duration? How child was in themselves? How did you manage this? What happened next? Feelings? *Did you take the child go to the GP/walk in centre/A&E? What did the GP/staff you spoke to advise? Did the GP/staff indicate what treatment for appendicitis might involve?*

2. **Can you talk me through what happened when you got to the hospital?**

Prompts: What was said, did you understand what was being said? Who did you speak to? How you/your child was feeling at this point? What else was being done to help? What was said about treatments? Thoughts/feelings?

Thoughts about the CONTRACT study

3. **What were your initial thoughts about the CONTRACT research study?**

Prompts: Who first mentioned the study/how did you first hear about it? What did you think/feel when you were first heard about it? Was there anything you/child liked about it – tell me about this? Was there anything you/child worried about?

How staff explained the study and acceptability of patient information & recruitment process:

4. **What did you think about how the study was explained?**

Prompts: What was said about it? Was there anything unclear or surprising? What questions did you have/did you ask these/were they answered? Did you feel people were able to take the time you/your child needed? Were they interested in what you/your child thought? What other information did you get about the study – verbal and written (PIS/IPAD video)? Did you read/watch it? What did you think of it? Did it give you the information you needed: enough information/too much? Were there things you thought they had forgotten to include? Did you have a chance to ask to about/look for information from other sources or not? If so, what information/which sources?

5. **What did the [nurse/surgeon/doctor] tell you about the two treatments in CONTRACT?**

Prompts: When/Where did you find this out? What did they say? What did you already know? What did you think? Depending on which treatment they talk about first: What did [they] mention about the other treatment? What there anything said that wasn't very clear? What did you think? Was it explained what was going to happen next? Feelings? Did you discuss the possibility of antibiotics not working? What was your understanding of this? What did you think about this? (Prompt: if discussed as same, prompt a bit further. Was your concern that they wouldn't work to treat [child] now or did you worry the appendicitis might come back in future?)

6. **What were the most important messages conveyed to you during the discussion with [nurse/surgeon/doctor] about the research study?**

Prompts: Treatment plan? Benefits? Risks? Recordings? Recovery? Did you feel it was you/your child's decision? Was there ever a sense of pressure?

7. **What did you think about having treatments allocated by randomisation, i.e. by chance?**

Prompts: How do you feel about this way of deciding what treatment you get? Were you okay to be randomised? Did you wonder why this is done? Did you think you were likely to get one treatment rather than the other? Did you feel like the team may have preferred one treatment over another for your child? Why? Is there a better way – could you tell me about more about your thoughts on how this would be better?

Reasons for accepting/declining participation [Use as applicable for those who agree, decline study/allocation]

8. **What did you think about when deciding whether or not to take part in the study?**

Prompts: Treatments offered? Randomisation? What did you already know? Favoured a particular treatment? Worries? Benefits? Time pressures? Any other pressures? Wider family views? Did you think about the study in terms of helping other people or not?

What do you think (recruiter) thought about the study? Did you get an impression whether (recruiter) thought one treatment or another would be more/less suited to (child)?

9. **Could I ask about how you decided not to take part in the study?**

Prompts: Would you tell me about what influenced your decision? Timing of request to take part? Timing of study? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know? Feelings? Expectations? Worries?

10. **What did you think when you were told you got [allocated group]?**

Prompts: How did you feel? Was it what you expected/wanted? What do you think about the treatments [allocated group] offered in this study?

Use depending on whether or not the family dropped out shortly after randomisation
I understand you decided to withdraw at randomisation – could you tell me about that decision? What would you have done if allocated the other treatment? Favoured a particular treatment? What did you already know? Randomisation? Expectations? Worries? Issues over participation? Engagement?

Use if family withdrew some hours or days after randomisation

11. **Could I ask about how you decided to stop participating in the study [withdraw]?**

Prompts: Would you tell me about what influenced your decision? Feelings? Expectations? Worries? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know? Timing of dropout from study?

Experience of treatment over time and recovery

12. Tell me about the treatment you/your child received?

Prompts: How was the [child's name] in the hours after the operation/the antibiotics were started. What was been good/bad about the treatment during that time? Would you change anything about it? If so what? How was it explained to you about what to expect? Is the treatment appropriate for someone of your/your child's age?

IF ANTIBIOTIC FAILURE…

Why did [child's name] have surgery after being randomised to antibiotics? Did you request surgery or did the doctor/nurse suggest that it would be best? What was the reason for this? What did you/they look out for when deciding to operate? How long between randomisation to antibiotics and the decision to operate? How long did you wait for an operation after it had been decided?

13. What has happened since the [surgery/antibiotic administration]?

Prompts: How was the [child's name] in the days after the operation/the antibiotics were started. What is good/bad about it in the longer term? Would you change anything about it? If so what? What did you expect recovery to be like? What were the main ways appendicitis affected you/your child? How did you know/what did you look out for to tell if the treatment was helping you/your child (symptoms/condition/life)? If you were telling someone who has never had appendicitis before what it's like to have it/have a child with appendicitis how would you describe it? How are they doing now – any problems? Are there any activities that s/he is not yet able to do? How will you know when they are fully recovered? What kind of things have you/they been worried about? Did the doctor explain that families that participate in CONTRACT will be followed up? Do you remember what was explained? How do you/your child feel about follow up? School? Home life? Life in general?

And finally

14. What do you think now about being involved in the CONTRACT study?

Prompts: Now a bit of time has passed, would you make the same decision again? Would you recommend it to a friend/family in the same situation? What do you think about the study for other children of your child's age? Thoughts on being recorded?

15 Is there anything else you would like to tell me?

Prompts: About the study? Randomisation? Taking part in research in general? Are there any questions you would like to ask?

Thank you for taking part in this sub-study!

CONTRACT: Interview Topic Guide Adapted for children (8-11yrs) and young people (12-15yrs)

v6.0 05/12/2017

CONTRACT

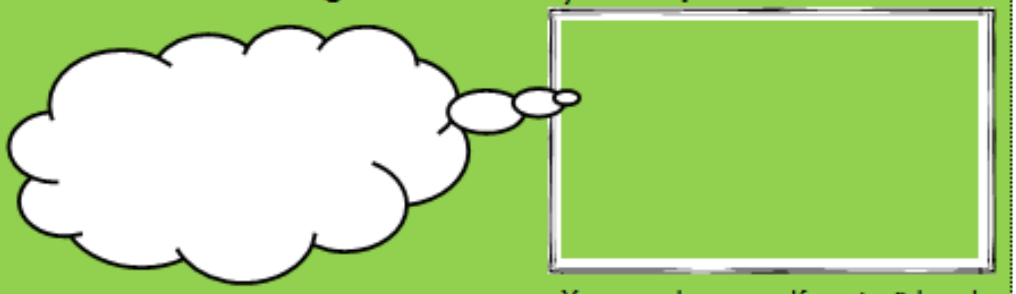
'What did you think about how the CONTRACT research study was explained to you?'

CONTRACT

'What did you think about when deciding to take part or not?'

CONTRACT

'What did you think when you got told you were having antibiotics/an operation?



You can draw a self portrait here!

CONTRACT

'Can you tell me about the treatment you had?'

CONTRACT

'What has happened since you had your treatment?'

CONTRACT

'What do you think now about being involved in the CONTRACT research study?'

Antibiotics

Surgery

CONTRACT communication (qualitative) sub-study
Topic Guide children (8-11yrs) / young people (12-15yrs)

v6.0 05/12/2017
Introductions, icebreakers & 5 minutes general chat.
Colouring or would they like to draw a picture?

Pass [adapted topic guide] to participant (age 8-11yrs) so they can write/draw in booklet and either keep it or hand it back to the researcher at the end of the interview.

Thoughts about the CONTRACT study

1. **What did you think when you were first told about the CONTRACT research study?**

Prompts: When were you told about it? How were you feeling when you were told about it? Was there anything you liked about it – tell me about this? Was there anything you didn't like? Was there anything that worried you about it?

2. **What did the doctor or nurse tell you about the two treatments in the study?**

Prompts: When/Where did you find this out? What did they say? What did you already know? What did you think? Depending on which treatment they talk about first: What did [they] mention about the other treatment? What there anything said that wasn't very clear? What did you think? Was it explained what was going to happen next? Feelings?

3. **What did you think about how the CONTRACT research study was explained to you? If they struggle to remember ask if you can show the video]**

Prompts: What was said about it? Was there anything unclear or surprising? What questions did you have/did you ask these/were they answered? Did you feel you had enough time to decide? Were they interested in what you thought? What other information did you get about the study – verbal and written (PIS/IPAD video)? Did you read/watch it? What did you think of it? What did it tell you? Did it give you the information you needed: enough information/too much? Were there things you thought they had forgotten to include? Is there anything we could do to improve how we explained the study to make it better for other patients in future?

4. **What did you think about when deciding to take part or not?**

Prompts: Treatments offered? Randomisation? What did you already know? Favoured a particular treatment? Worries? Benefits? Time pressures? Any other pressures? Wider family views? Did you think about the study in terms of helping other people or not? What do you think the most important message was?

5. **What did you think when you were told you were having antibiotics/an operation?**

Prompts: How did you feel? Was it what you expected/wanted? What do you think about the treatments [allocated group] offered in this study? I understand you decided to withdraw at randomisation – could you tell me about that decision? What would you have done if allocated the other treatment? Favoured a particular treatment? Did you feel like the team may have preferred one treatment over another for you? Why? What did you already know? Randomisation? Expectations? Worries? Issues over participation? Engagement?

6. **Can you tell me about the treatment you had?**

Prompts: What has been good/bad about it? Would you change anything about it? If so what? How was it explained to you? Is the treatment appropriate for someone of your/your child's age?

7. **What has happened since you had your treatment]?**

Prompts: What is good/bad about it? Would you change anything about it? If so what? What did you expect recovery to be like?
What were the main ways it affected you? How did you know/what did you look out for to tell if the treatment was helping you (symptoms/condition/life)? If you were telling someone who has never had appendicitis before what it's like to have it how would you describe it? How are you/they doing now? How will you know when you/they are fully recovered? What kind of things have you/they been worried about? Any side effects? Did the doctor explain that families that participate in CONTRACT will be followed up with a few more appointments to see how you're getting on? Do you remember what was explained? How do you feel about follow up? School? Home life? Life in general?

8. **What do you think now about being involved in the CONTRACT research study?**

Prompts: Would you do it again? Would you recommend it to a friend/family in the same situation? What could we do to improve the study & make it better? What do you think about the study for others your age?

Further questions depending on age and maturity

9. **What were the most important messages that the [doctor or nurse] told you about the study?**

Prompts: Treatment plan? Benefits? Risks? Recordings? Recovery? Did you make this decision with your parent(s)/carer(s) or did they decide for you? Did you sign something, (assent) what did you think about this?

10. **What did you think about having treatments chosen by randomisation? [explain randomisation as 50:50 chance of being in one group or the other]**

Prompts: How do you feel about this way of deciding what treatment you get? Were you okay with this? Is there a better way we could explain this to you? Did you wonder why this is done? Did you think you were likely to get one treatment rather than the other?

11. **Could I ask about how you decided not to take part in the study?**

Prompts: Would you tell me about what influenced your decision? Timing of request to take part? Timing of study? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know? Feelings? Expectations? Worries?

12. **Could I ask about how you decided to stop participating in the study [drop-out]?**

Prompts: Would you tell me about what influenced your decision? Feelings? Expectations? Worries? Treatments offered? Randomisation? Favoured a particular treatment? What did you already know? Timing of dropout from study?

13. **Is there anything else you would like to tell me?**

Prompts: About the study? Randomisation? Taking part in research in general? Are there any questions you would like to ask?

Thank you for taking part in this sub-study!

CONTRACT: Recruitment training methods

Members of three surgical teams were responsible for recruiting to the CONTRACT RCT. The total number of surgeons recruiting into the trial was not known by the qualitative team, because study consent forms were only sent to the research team when families also opted into the nested qualitative communication study. Three initial face-to-face group training session was carried out with 29 surgeons and research nurses supporting recruitment. Recruiters' past experience of recruiting to RCTs was not known. Recruitment was split into three 'phases' during the CONTRACT RCT, with each of the three training sessions conducted at the beginning of either, phase one, two or three of recruitment:

Phase one of recruitment months 1-4.

Phase two of recruitment months 5-8.

Phase three of recruitment months 9-12.

Phase one training included a generic PowerPoint presentation, informal group discussions, and role-play activities. Phases two and three included tailored PowerPoint presentations, and specific examples from previous months recruitment consultations:

Generic training topics: Phase 1
Recruitment issues for RCTs
Public perceptions of RCT research
Discussing RCTs with families and exploring treatment preferences
Group work
Role play / demonstration
Overview of CONTRACT Communication study
Communication study: How will it work?
Digital recorders
Questions
Round up and future training sessions

Tailored training topics: Phase 2
Recruitment to CONTRACT: How are we doing so far?
CONTRACT Communication study quiz (terminology)
Consultations exemplary in terms of…
Is there room to be a bit more positive about research and about CONTRACT? Words suggestive of burden
Participation positives
More balanced language for treatment arms…
Terminology for study arms
Exploring reasons and beliefs underlying preferences
Balancing treatment preferences
Past experience: Previous bad experience of appendicitis
Randomisation: Examples of good explanations
Families' questions
Introducing the recording…
Questions

Tailored training topics: Phase 3
Feasibility Study Progress
Thank you to recruiters
Communication Study Progress
Health professional feedback leads to change
Consultations exemplary in terms of…
R.C.T. Fortunes!
CONTRACT Consultation Process
Describing randomisation
Antibiotics: Recurrence & managing expectations
Surgery: Surgical risks are often neglected
Words have power (terminology)
Exploring treatment preferences
Balancing treatment preferences
Families' questions
Questions

Recruiters were again provided with a 'Hints and Tips' document (CONTRACT: Tips for Recruitment and informed consent) adapted and developed for use, drawing upon good practice from the SMILE, MAGENTA and FITNET-NHS RCTs. After the second training session a second document was developed (see: CONTRACT: Recruitment Flowchart) because surgeons reported that they also wanted a step by step guide of the documents and equipment needed to conduct the consultation, (e.g. digital recorder, PILs, consent forms and iPad) and the sequence in which they

should conduct each task (e.g. introducing the RCT, verbal consent, recording the discussion, showing the iPad video). Many surgeons recruited to the RCT infrequently, so wanted all this information in one document. The flowchart also provided information on the inclusion/exclusion criteria, and how to explore negative past experience of appendicitis, because this was a common reason provided by families who declined the RCT.

CONTRACT: Tips for Recruitment and informed consent

v2.0 30/06/2017

CONTRACT
CONservative TReatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

Hints and Tips for Recruiters

This sheet offers a few suggestions that may help with recruitment and consent to CONTRACT.

CHECKLIST - What do I need?
☑ Digital recorder
☑ IPad with video
☑ CONTRACT information sheet
☑ CONTRACT consent form

Before discussing the study with families

- Consider the best time is to discuss the study with the family.
- Out of hours you may not want to have detailed discussions about the study. However, families might have questions about treatment, even in the middle of the night. In discussing treatment a brief mention about CONTRACT may be helpful.

Audio-recording the discussion(s)

- Please audio-record all discussions with patient/family (including all stages of the discussions where there are several with the same family, and also when the allocated treatment is revealed), providing they are happy for you to do so. This gives us an insight into what works so we can help you and others to recruit effectively.
- In previous research, over 90% of families were willing to have their consultation recorded. Many forget the recorder is there whilst speaking and families often feel happy that they have contributed towards research.
- Families can initially provide verbal consent for the recording, and written consent to keep the recording can be sought at the end of the discussion(s). **Please say your name and the date at the beginning of each recording.**

Introducing the study to families

'I've got a research study I'd like to tell you about that is open to children like (child's name) with appendicitis. (Child's name) is eligible because he/she has suspected non-complicated appendicitis. As part of the research study, we'd like to record our discussion about the study. It's completely confidential and we use the recording to inform future communication with families about health research. Would you mind if we did that? You can also tell me at the end whether you're OK for us to keep the recording or not and I'll ask you to sign a consent form.'

Discussing the study with families

- Show families the IPad video - this is a really clear and consistent way to communicate the message.
- Present the study in a positive way - it is an opportunity for the family to take part in a study that could contribute towards improving paediatric treatment in future. The treatments being compared are both good treatments.

Key steps...
After explaining the condition...

1. **Reassure** the family that there are **two treatment routes** that can be used to treat acute appendicitis in children - antibiotics and surgery – and studies have shown they are both effective.

2. Establish that there is **current uncertainty**: 'We want to find out whether children/young people with appendicitis are better off being treated with antibiotics or with surgery.

Current evidence

Antibiotics: Using a non-operative approach, the child would avoid the trauma, physiological stress, psychological distress and physical scarring of an operation. Based on the research that has been done so far, we believe the risk of recurrence is low; for every 100 patients, we estimate around 14 will have a recurrence in the first year (or 1 in 7 children). The potential benefit of antibiotic treatment is that your child may avoid an operation and general anaesthesia altogether.

Appendicectomy: Although appendicectomy avoids recurrence, it carries several risks. For every 100 patients who undergo surgery, up to 25 (1 in 4 people) will experience complications (including wound infection, intra-abdominal abscess, and adhesional small bowel obstruction), 4-5 will be readmitted to hospital (1 in 20-25 children), and 10 patients may show a healthy appendix, which means that the surgery was not necessary for 1 in 10 people.

3. Give a **balanced view** of each **treatment** (refer to "Current evidence" box)
   - People often associate studies with experimental treatments so it may help to emphasise to families that both treatments in CONTRACT are currently used widely and well understood.
   - Present **balanced information** about both treatments and **spend equal time** discussing the benefits and drawbacks of each. So far, we've found that the drawbacks of surgery are sometimes not prominent in the discussions, whereas, the drawbacks of antibiotics are very prominent.
   - If parents / families do not voice these spontaneously, try to elicit their concerns/preferences with an open question, *'What are your initial thoughts now you've heard about the study?'*
   - Gently find out the reasons why a patient/family prefers/is concerned about one option over the other with an open question, '*What makes you think that's the best treatment?*' Exploring families' treatment preferences and the beliefs underlying these will enable you to correct any misunderstandings and ensure they understand both treatments well enough to make an informed decision.
   - Exploring treatment preferences also allows you to tailor so that information is balanced in a personalised way.
   - It is completely fine to gently challenge preferences e.g. if someone has a preference for surgery then the potential benefits of antibiotics can be emphasised. Similarly, if someone has had negative experiences of appendicitis in the past, it is OK to explore this. Negative experiences of complicated appendicitis in an adult, or a case that happened many years ago, may not be relevant to the child's current situation.

4. Explain the **study procedures**, providing the family with time to discuss CONTRACT among themselves, read the leaflets and come back to you with any questions. These are some key points to cover:
   - They will be asked to sign a consent form - avoid emphasising this as a burden.
   - Randomisation (including rationale – please see below for tips).
   - Treatment procedures (e.g. children may want to know how will the antibiotics be administered)
   - Follow-ups (no detail at this stage, just that they will have them)
   - Data protection – all details are kept confidential
   - Request for discussion with CONTRACT Communication Study Researcher – **we are particularly interested in speaking with families who have declined CONTRACT**
   - Remind the patient that regardless of which treatment they are allocated to, they will receive the best possible care and the health professional treating them will be experienced in the treatment provided.

5. Explain the **study purpose**: 'CONTRACT is a feasibility study to help us do a larger study comparing surgery and antibiotics. We need evidence from large studies before we can change how children with appendicitis all over the UK are treated in future.'

Describing randomisation

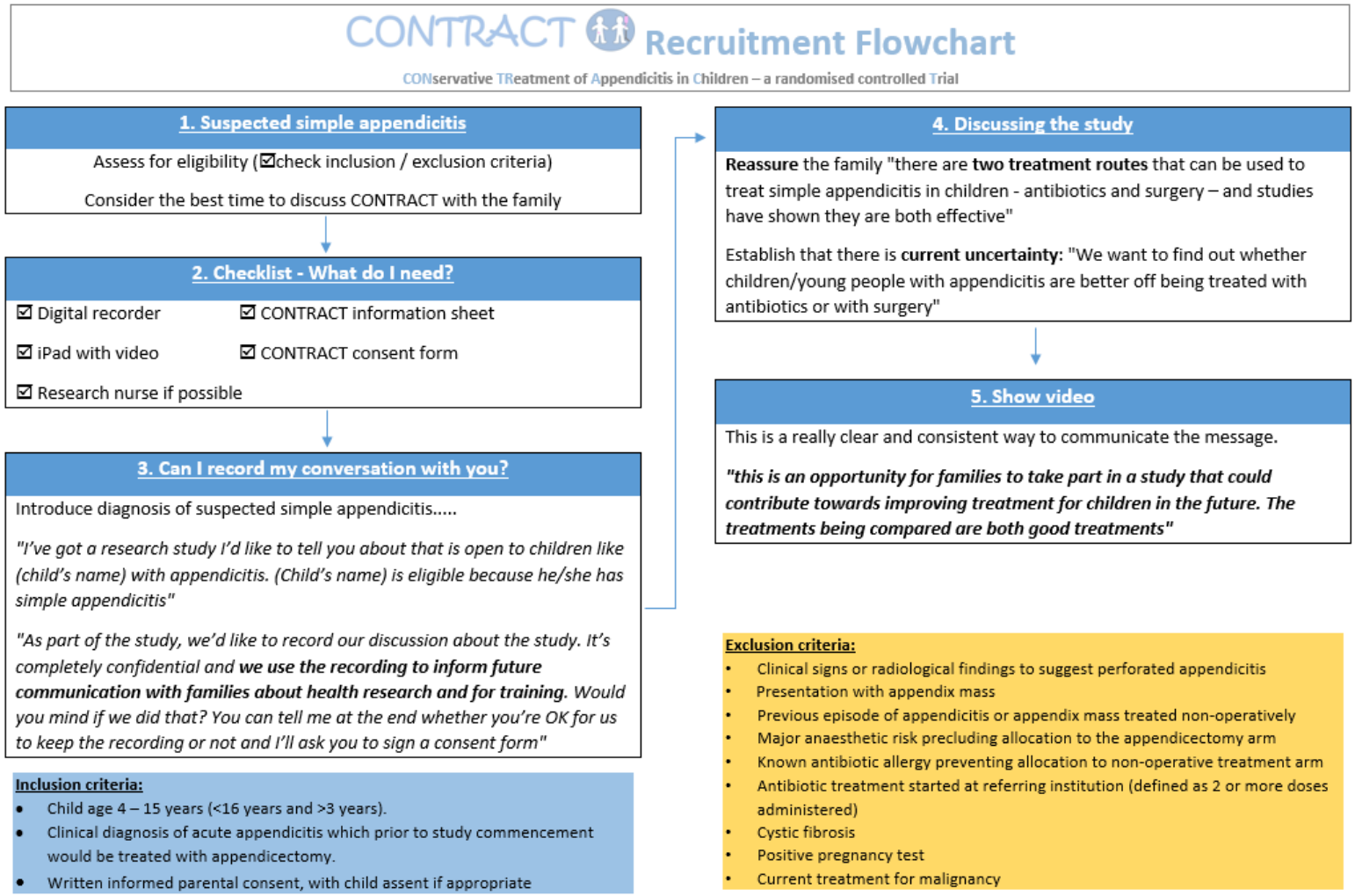
- Avoid terms such as 'toss of a coin 'or 'decided by a computer' to explain randomisation. Instead explain that if the patient were to join the study, they would have an equal chance of having an operation or the antibiotics.
- Explain the rationale for randomisation (only way to avoid bias). Cover the key points: we need a fair comparison between the two treatments/groups. The only way to do this is to use randomisation to produce similar groups.

'We know both treatments are good but want to know which is better. To do this we need to compare the two treatments in similar groups of patients. The only way to make sure that the groups are as similar as possible is to put people into groups by a process called randomisation. This means that if you and [name] take part in CONTRACT, you will have an equal chance of having the operation or the antibiotics. It is important that you only agree to take part if you are prepared to consider either treatment.'

Language/terms: Try using the word 'study', rather than 'trial'. Avoid loaded terminology (e.g. 'gold standard', 'experimental', 'the first/second treatment'). It's helpful to refer to antibiotics or surgery to emphasise equipoise.

CONTRACT: Recruitment Flowchart

V2. 18/09/2017



6. Elicit any concerns / questions about treatments

If parents / families do not voice these spontaneously, with an open question:

"What are your initial thoughts now you've heard about the study?"

"What are your thoughts about these treatments?"

Gently find out the reasons why a patient/family prefers/is concerned about one option with an open question:

"What makes you think that's the best treatment?"

- Exploring treatment preferences also allows you to tailor so that information is balanced in a personalised way.
- You are not persuading, but ensuring families are fully informed
- **[see current evidence below & hints and tips doc]**

7. A negative experience of perforated appendicitis?

It is OK to explore this. Negative experiences of complicated appendicitis in an adult, or a case that happened many years ago, may not be relevant to the child's current situation.

"we do not think [name] has a perforated appendicitis but simple appendicitis otherwise he/she would not be eligible for CONTRACT"

"All patients in CONTRACT are very closely monitored and anyone who is allocated to antibiotics who is not improving as we would expect will be offered an appendicectomy"

8. Describing randomisation

- *"We know both treatments are good but want to know which is better. To do this we need to compare the two treatments in similar groups of patients"*
- *"In order to do a comparison, what you need is two groups and for them to be selected not by us saying, oh this patient should have surgery, that patient should have antibiotics"*
- *"The only way to make sure that the groups are as similar as possible is to put people into groups by a process called randomisation"*
- *"What that means is that there's an equal chance of either having antibiotics as the treatment or surgery as the treatment"*

9. Explain the study procedures

☑ Follow-ups 6wk, 3mth, 6mth

☑ Data protection – all details are kept confidential

☑ Request for discussion with sub-study Researcher – **particularly families who decline CONTRACT**

"CONTRACT is a feasibility study to help us do a larger study comparing surgery and antibiotics. We need evidence from large studies before we can change how children with appendicitis all over the UK are treated in future"

"All patients in CONTRACT are very closely monitored....."

10. Give them time to consider the information

Give the family **time to discuss** CONTRACT among themselves, **read the leaflets** and come back to you with **any questions**.

"Regardless of which treatment [name] is allocated to, they will receive the best possible care and the health professional treating them will be experienced in the treatment provided"

11. Obtaining consent

Please ask the parent/guardian to initial each box they are happy with and to sign the consent form.

- Boxes 1-8 are linked to the **CONTRACT Feasibility Study**.
- Boxes 9-10 are linked to the **CONTRACT Communication Study**.

Families can participate in the CONTRACT Communication Study *only*, the CONTRACT Feasibility Study *only*, *both studies*, or *neither study*.

12. How to randomise a patient

You will need your TENALEA username and password and:

- **the age of the child**
- **duration of symptoms (onset of pain until now)**
- **gender**
- **patient initials**

Once the consent form is signed log in to: **https://prod.tenalea.net/stn/dm/**
Click on CONTRACT study on left hand side
Then click on your local PI name
Then click on add patient
Complete the details and click 'SUBMIT'
If you can, print out the next page or at least note down the randomisation number

Current evidence

Antibiotics:

Using a non-operative approach, the child would avoid the trauma, physiological stress, psychological distress and physical scarring of an operation.

Based on the research that has been done so far, we believe the risk of recurrence is low; for every 100 patients, we estimate around 14 will have a recurrence in the first year (or 1 in 7 children).

The potential benefit of antibiotic treatment is that your child may avoid an operation and general anaesthesia altogether.

Appendicectomy:

Although appendicectomy avoids recurrence, it carries several risks.

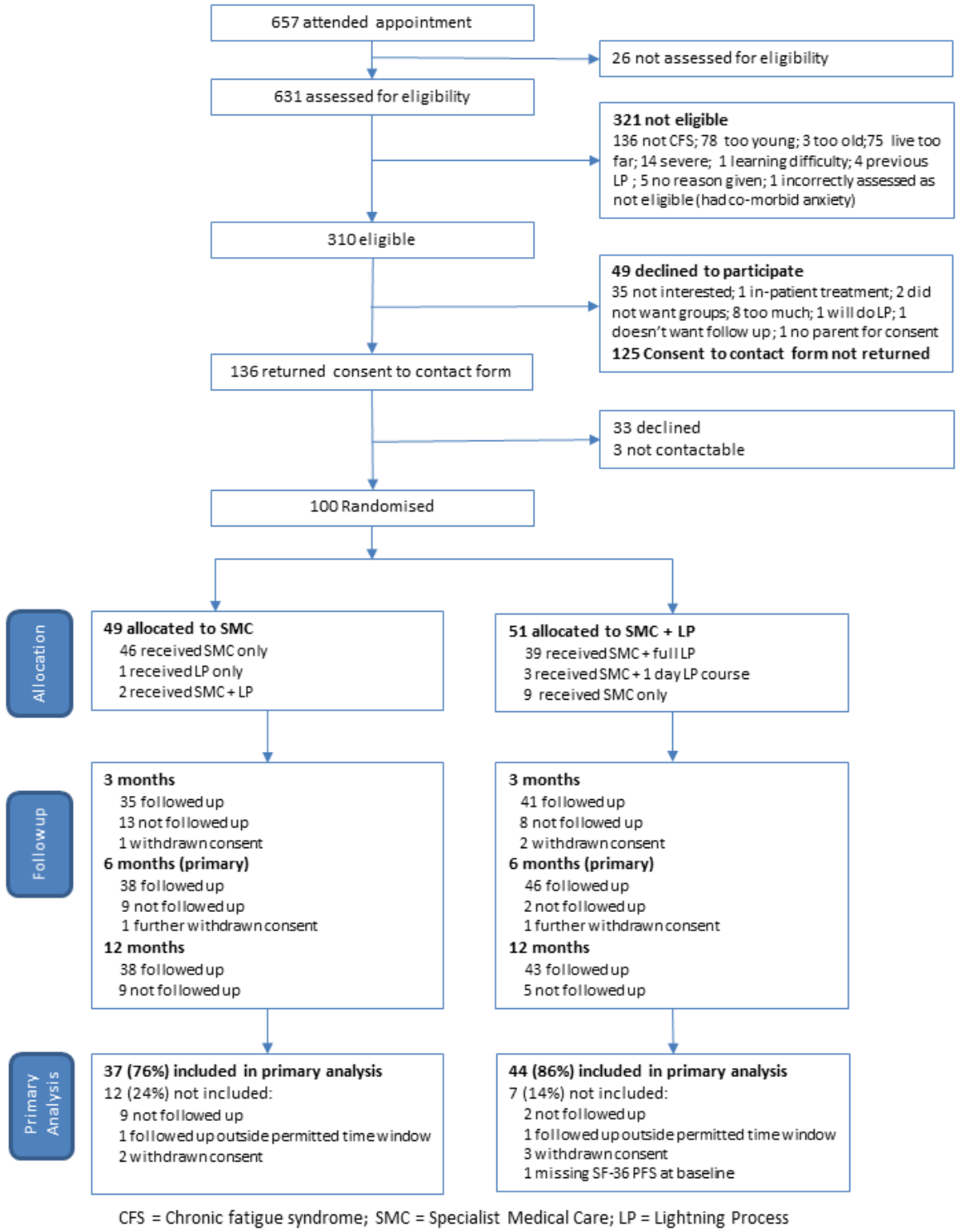
For every 100 patients who undergo surgery, up to 25 (1 in 4 people) will experience complications (including wound infection, intra-abdominal abscess, and adhesional small bowel obstruction),

4-5 will be readmitted to hospital (1 in 20-25 children),

10 patients may show a healthy appendix, which means that the surgery was not necessary for 1 in 10 people.

Appendix 7: CONSORT Diagrams

SMILE: CONSORT diagram



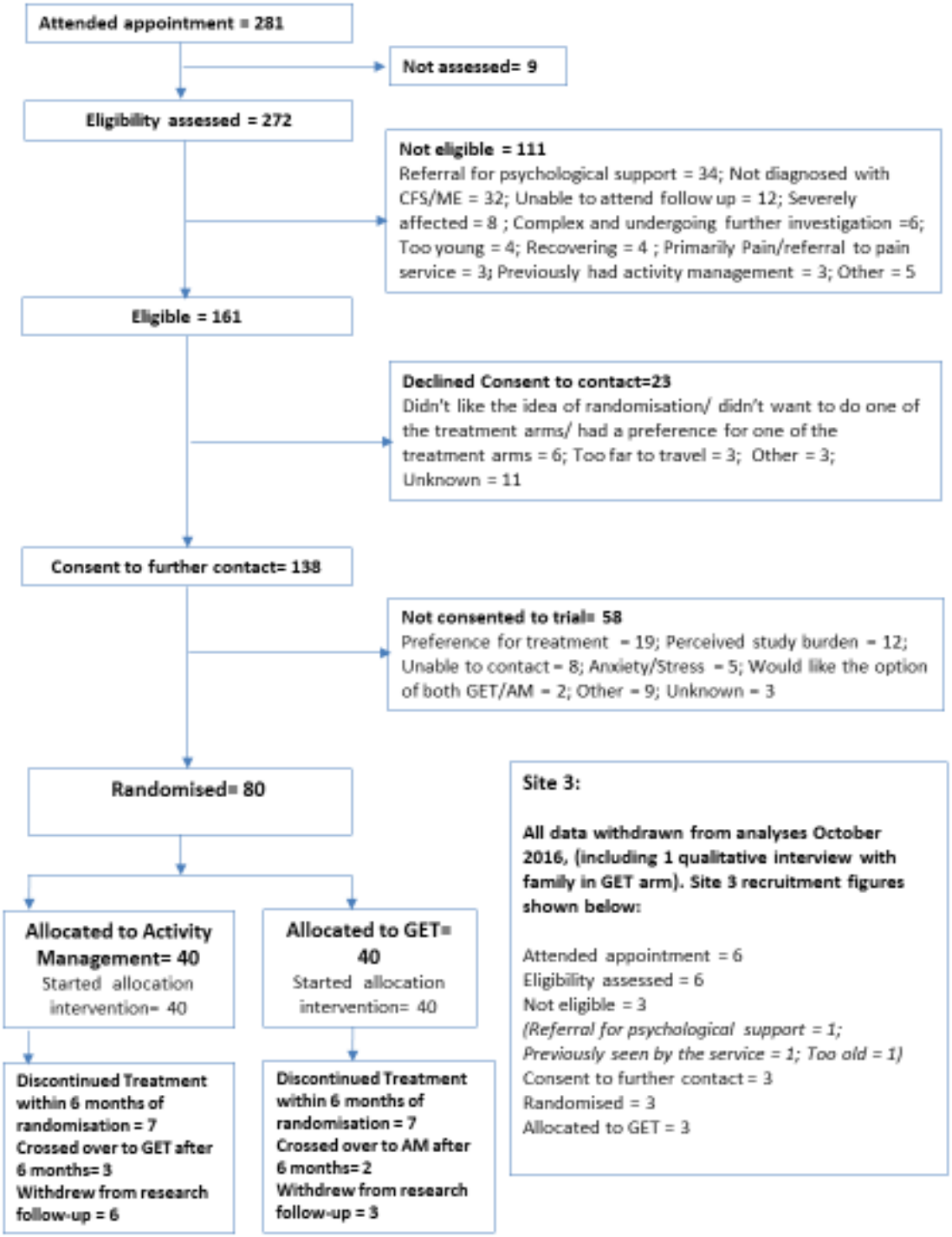
CFS = Chronic fatigue syndrome; SMC = Specialist Medical Care; LP = Lightning Process

SMILE: Declined after consent to contact

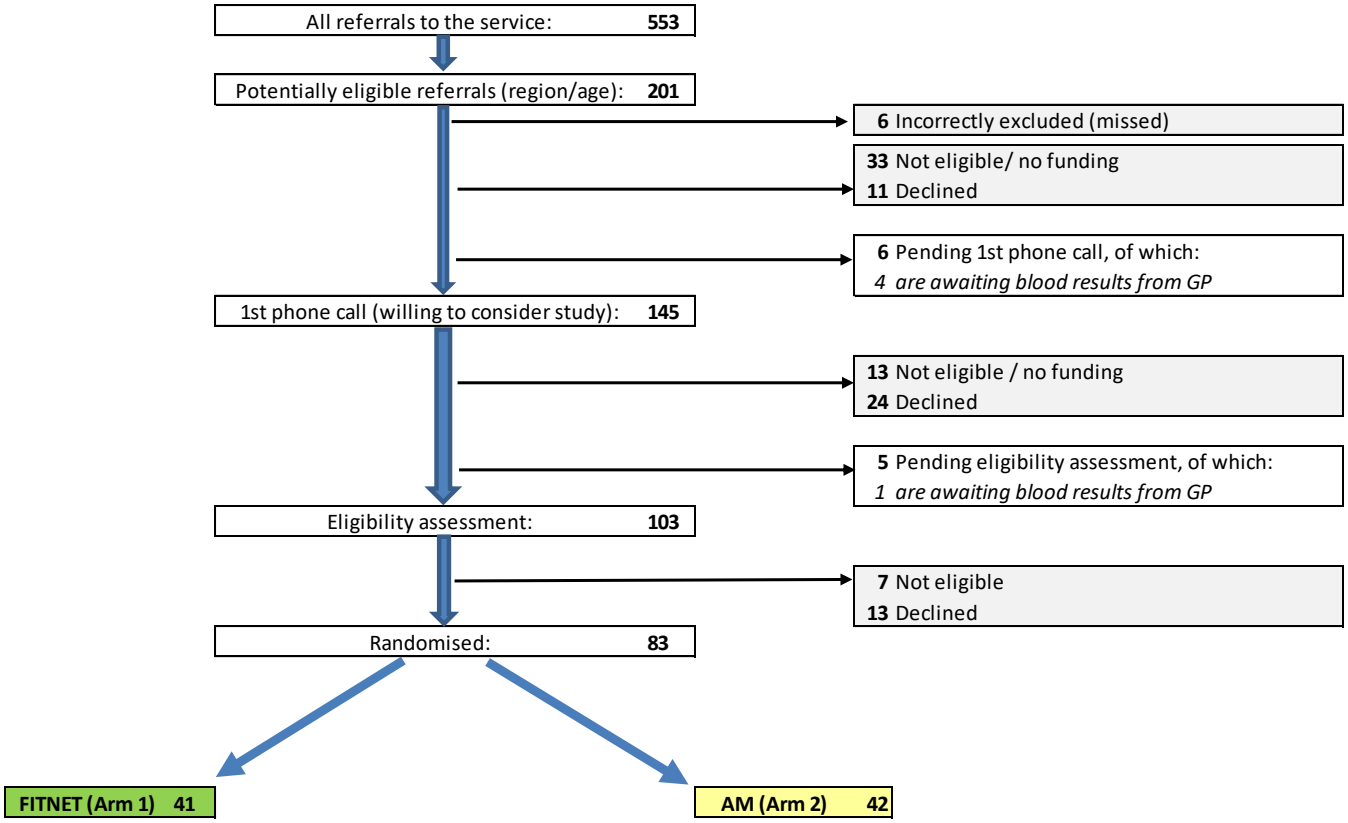
(When recruiter made contact by telephone)

Reason for decline	Returned consent to contact: Declined
Perceived study burden	9
Preference for treatment	9
Too much at moment	8
Reason not known	4
Too unwell	3
TOTAL DECLINED	**33**

MAGENTA: CONSORT diagram



FITNET-NHS: CONSORT diagram

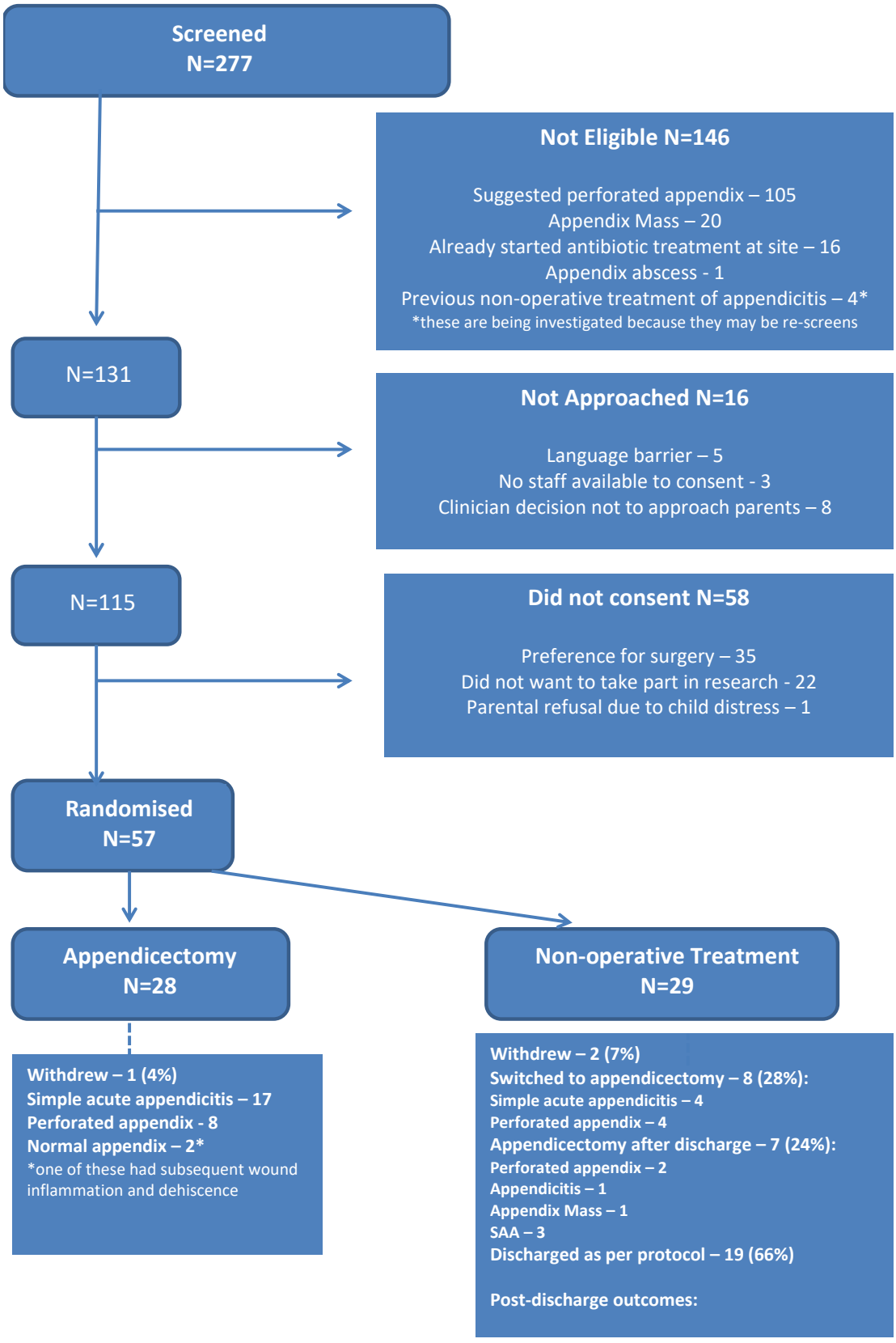


Of those potentially eligible (n=201) participants were excluded from the RCT at three time points due to ineligibility/no funding (n = 53). Therefore, the total number of eligible participants = 148

FITNET-NHS Excluded and declining participants

	Pre first contact	First phone call	Eligibility assessment	TOTAL	*% of those not in trial*	% of total referrals
TOTAL NOT IN TRIAL (ANY REASON):	**50**	**37**	**20**	**107**	*100%*	53%
TOTAL EXCLUSIONS	**33**	**13**	**7**	**53**	*50%*	26%
EXCLUSION: Local specialist service	9	9	2	20	*19%*	10%
EXCLUSION: Referred for diagnosis/ second opinion (req face to face)	4	2	0	6	*6%*	3%
EXCLUSION: Diagnosis: Not CFS (includes other cause for fatigue)	3	0	3	6	*6%*	3%
EXCLUSION: Diagnosis: Not disabled by fatigue	0	0	1	1	*1%*	0%
EXCLUSION: No bloods - Needlephobic	2	0	0	2	*2%*	1%
EXCLUSION: No bloods - none returned within 6 weeks of request	1	0	0	1	*1%*	0%
EXCLUSION: Unable to do FITNET modules/ Skype - give reason (e.g. no computer/ not computer literate - parent or child/ learning difficulties)	0	0	1	1	*1%*	0%
EXCLUSION: Pregnant at assessment	0	0	0	0	*0%*	0%
EXCLUSION: Age	7	1	0	8	*7%*	4%
EXCLUSION: Not funded	5	0	0	5	*9%*	2%
*OTHER exclusion/decline (give reason)*****	2	1	0	3	*3%*	1%
OTHER: Inapproriately excluded	6	0	0	6	*6%*	3%
TOTAL DECLINED	**11**	**24**	**13**	**48**	*45%*	24%
DECLINED: Want face to face appt	7	10	7	24	*22%*	12%
DECLINED: Perceived study burden	0	2	0	2	*2%*	1%
OTHER: Family/patient away	0	1	0	1	*1%*	0%
*DECLINED: Declined TRIAL - other reason (please state if known)***	0	7	1	8	*7%*	4%
*DECLINED: Declined TREATMENT (give reason if known)****	4	4	5	13	*12%*	6%
OTHER: Uncontactable	0	0	0	0	*0%*	0%

CONTRACT CONSORT diagram



[Reference: Moher, D., et al., CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ, 2010. 340: p. c869.]

Appendix 8: Monthly recruitment Figures

MAGENTA

Month	Recruited	Declined all	Total by month	Cumulative
1	7	3	10	10
2	3	5	8	18
3	9	3	12	30
4	8	5	13	43
5	5	7	12	55
6	3	4	7	62
7	12	3	15	77
8	7	5	12	89
9	8	8	16	105
10	7	10	17	122
11	8	14	22	144
12	3	14	17	161
13	8	3	11	
Total	**80**	**81**	**161 (1st 12 months)**	

FITNET-NHS

Month	Recruited	Declined all time points	Total by month	Cumulative
1	1	5	6	6
2	6	9	15	21
3	7	5	12	33
4	10	2	12	45
5	11	6	17	62
6	3	1	4	66
7	8	1	9	75
8	13	3	16	91
9	8	7	15	106
10	7	2	9	115
11	3	1	4	119
12	6	6	12	131
13	9	4	13	
Total	**83**	**48**	**131 (1st 12 months)**	

CONTRACT

Month	Site D			Site E			Site F			Total [Sites D,E&F]			Cumulative Total	
	Approached	Recruited	%	Approached	Recruited	%	Approached	Recruited	%	Approached	Recruited	%	Approached	Recruited
1	2	2	100%	7	3	43%	5	2	40%	14	7	50	14	7
2	3	1	33%	1	1	100%	1	0	0%	5	2	40	19	9
3	4	2	50%	4	0	0%	1	0	0%	9	2	22	28	11
4	5	3	60%	1	0	0%	3	0	0%	9	3	33	37	14
5	6	3	50%	2	1	50%	4	3	75%	12	7	58	49	21
6	6	1	17%	3	2	67%	2	0	0%	11	3	27	60	24
7	7	3	43%	3	2	67%	4	3	75%	14	8	57	74	32
8	5	2	40%	1	1	100%	1	1	100%	7	4	57	81	36
9	3	0	0%	5	2	40%	1	1	100%	9	3	33	90	39
10	5	2	40%	3	3	100%	0	0	0%	8	5	63	98	44
11	2	2	100%	7	6	86%	2	0	0%	11	8	73	109	52
12	4	4	100%	0	0	0%	2	1	50%	6	5	83	115	57
	52	**25**	**48%**	**37**	**21**	**57%**	**26**	**11**	**42%**	**115**	**57**	**50%**	**115**	**57**

CONTRACT: Reasons for decline by site at 9 months (% preference)

	Site D	Site E	Site F	Total
Preference for surgery	21	3	5	29
Does not want to take part in research	3	11	7	21
Other – patient in distress	0	1	0	1
Randomised	17	12	10	39
Unable to provide informed consent due to language barrier	**3**	**1**	**1**	**5**
No staff available	**2**	**0**	**0**	**2**
Clinician decision not to approach	1	2	2	5
	47	**30**	**25**	**102**
% PREF	**45%**	**10%**	**20%**	

Appendix 9: Qualitative interview samples all trials (Family interviews)

SMILE: Family interview sample

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	status in trial	Treatment group	Site ID
Young person S4 Mum S4	Male	12	7	77	Recruited	Specialist Medical Care	S
Young person S88 Mum S88	Female	17	10	13	Recruited	Specialist Medical Care	S
Young person S2 Mum S2	Female	14	6	63	Recruited	Specialist Medical Care	S
Mum S33	Female	15	3	135	Crossed to Lightning Process	Specialist Medical Care	S
Young person S35 Mum S35	Female	12	10	20	Recruited	Specialist Medical Care	S
Young person S38 Mum S38	Female	16	10	26	Recruited	Specialist Medical Care	S
Young person S5 Mum S5	Female	13	5	273	Recruited	Specialist Medical Care plus Lightning Process	S
Young person S36 Mum S36	Female	13	4	137	Recruited	Specialist Medical Care plus Lightning Process	S
Young person S9 Mum S9	Female	12	4	99	Recruited	Specialist Medical Care plus Lightning Process	S
Young person S12 Mum S12	Female	15	5	223	Recruited	Specialist Medical Care plus Lightning Process	S
Young person S7 Mum S7	Male	13	4	79	Recruited	Specialist Medical Care plus Lightning Process	S

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	status in trial	Treatment group	Site ID
Young person S34 Mum S34	Male	15	9	108	Recruited	Specialist Medical Care plus Lightning Process	S
Young person S8 Mum S8	Female	16	3	58	Recruited	Specialist Medical Care plus Lightning Process	S

MAGENTA: Family interview sample

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person M35 Mum M35 Dad M35	Female	17	9	36	Crossed to Graded Exercise Therapy	Activity management	M
Young person M51 Mum M51	Female	14	10	105	Crossed to Graded Exercise Therapy	Activity management	M
Young person M65 Mum M65	Male	8	3	30	Recruited	Activity management	M
Young person M9 Dad M9	Male	14	5	154	Recruited	Activity management	M
Mum M23	Male	12	6	70	Recruited	Activity management	M
Young person M72 Mum M72	Male	10	9	154	Recruited	Activity management	M

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person M88 Mum M88	Female	13	4	182	Recruited	Activity management	M
Young person M99	Female	16	9	173	Recruited	Activity management	M
Young person M60, Mum M60	Female	17	10	69	Recruited	Activity management	M
Young person M11, Mum M11	Female	11	6	86	Recruited	Activity management	M
Young person M129 Mum M129	Male	15	9	76	Recruited	Activity management	M
Young person M93 Mum M93	Female	13	5	38	Recruited	Activity management	M
Young person M29 Mum M29	Male	15	6	244	Withdrew from treatment	Activity management	M
Young person M2 Mum M2	Female	17	8	25	Withdrew from treatment & trial	Activity management	M
Young person M108 Mum M108	Female	14	10	39	Withdrew from treatment & trial	Activity management	M
Mum M52	Female	15	6	106	Declined	Care outside RCT	M
Young person M61 Mum M61	Female	15	10	9	Declined	Care outside RCT	M
Mum M87	Female	17	4	13	Declined	Care outside RCT	M
Mum M110	Female	12	3	8	Declined	Care outside RCT	M
Mum M98	Female	14	6	7	Declined	Care outside RCT	M

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person M34 Mum M34	Male	15	6	99	Crossed to activity management	Graded Exercise Therapy	M
Young person M25 Mum M25	Female	16	10	39	Recruited	Graded Exercise Therapy	M
Young person M5 Mum M5	Female	10	7	21	Recruited	Graded Exercise Therapy	M
Young person M3 Mum M3	Male	14	4	75	Recruited	Graded Exercise Therapy	M
Young person M16 Mum M16	Female	14	6	116	Recruited	Graded Exercise Therapy	M
Young person M20 Mum M20	Female	17	7	107	Recruited	Graded Exercise Therapy	M
Young person M43 Mum M43	Male	17	9	215	Recruited	Graded Exercise Therapy	M
Young person M49 Mum M49	Male	15	3	192	Recruited	Graded Exercise Therapy	M
Young person M115 Mum M115	Female	16	1	168	Recruited	Graded Exercise Therapy	M
Young person M1 Mum M1	Female	10	10	160	Recruited	Graded Exercise Therapy	M
Young person M109 Mum M109	Male	17	3	83	Recruited	Graded Exercise Therapy	M
Young person M64 Mum M64	Female	15	5	54	Recruited	Graded Exercise Therapy	M

FITNET-NHS: Family interview sample

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young Person F3 Mum F3	Male	15	10	80	Recruited	Skype activity management	F
Young Person F1 Mum F1	Female	12	7	75	Recruited	Skype activity management	F
Young Person F15 Mum F15	Female	12	6	189	Recruited	Skype activity management	F
Mum F9	Male	16	8	231	Recruited	Skype activity management	F
Young Person F22	Female	11	7	141	Recruited	Skype activity management	F
Mum F11	Female	13	4	131	Recruited	Skype activity management	F
Young Person F20 Mum F20	Female	13	6	121	Recruited	Skype activity management	F
Young Person F13 Mum F13	Female	15	8	97	Recruited	Skype activity management	F
Young Person F23 Mum F23	Female	16	8	83	Recruited	FITNET Online CBT	F
Young Person F25 Mum F25	Male	13	3	66	Recruited	FITNET Online CBT	F

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young Person F18 Mum F18	Male	13	8	229	Recruited	FITNET Online CBT	F
Young Person F27 Mum F27 Dad 27	Female	14	7	174	Recruited	FITNET Online CBT	F
Young Person F6 Mum F6	Female	13	9	210	Recruited	FITNET Online CBT	F
Young Person F10 Mum F10	Female	16	10	69	Recruited	FITNET Online CBT	F
Young Person F28 Mum F28 Dad F28	Female	15	4	132	Recruited	FITNET Online CBT	F
Young Person F21 Mum F21	Male	11	10	117	Recruited	FITNET Online CBT	F
Young Person F26 Mum F26	Male	11	5	140	Recruited	FITNET Online CBT	F
Young Person F24 Mum F24	Female	17	5	226	Recruited	FITNET Online CBT	F
Young Person F12 Dad F12	Female	16	8	126	Recruited	FITNET Online CBT	F
Young Person F19 Mum F19	Male	14	10	88	Recruited	FITNET Online CBT	F

CONTRACT: Family interview sample

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person CE6 Mum CE6	Male	11	1	28	Recruited	Antibiotics	CE
Young person CF20 Dad CF20	Male	7	7	25	Recruited	Antibiotics	CF
Young person CD9 Mum CD9 Dad D9	Male	12	2	56	Recruited	Antibiotics	CD
Young person CE7 Mum CE7	Male	14	10	32	Recruited - Recurrence: Continued with antibiotics	Antibiotics	CE
Young person CE4 Mum CE4 Dad CE4	Male	10	8	38	Recruited - Recurrence: Continued with antibiotics	Antibiotics	CE
Young person CE5 Mum CE5 Dad CE5	Female	9	10	33	Recruited - Recurrence: Revert to surgery	Antibiotics	CE
Young person CD1 Mum CD1	Female	10	3	34	Recruited - Treatment failure: Revert to surgery	Antibiotics	CD
Young person CD15 Dad CD15	Female	12	9	35	Recruited - Treatment failure: Revert to surgery	Antibiotics	CD
Young person CD10 Mum CD10	Male	6	9	20	Recruited - Treatment failure: Revert to surgery	Antibiotics	CD

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person CD21 Mum CD21	Male	7	5	48	Recruited - Withdrew from trial as felt child was getting worse	Antibiotics	CD
Young person CE19 Dad CE19	Male	11	3	55	Recruited	Appendectomy	CE
Young person CE23 Mum CE23	Male	8	3	34	Recruited	Appendectomy	CE
Young person F9 Mum CF9 Dad CF9	Female	8	10	51	Recruited	Appendectomy	CF
Young person CF13 Dad CF13	Male	7	9	88	Recruited	Appendectomy	CF
Young person CF19 Mum CF19	Female	6	8	43	Recruited	Appendectomy	CF
Young person CF11 Dad CF11	Male	13	5	117	Recruited	Appendectomy	CF
Young person CD2 Dad CD2	Female	11	2	39	Recruited	Appendectomy	CD
Young person CD5 Mum CD5	Male	9	10	49	Recruited	Appendectomy	CD
Young person CD18 Mum CD18	Male	9	8	28	Recruited	Appendectomy	CD
Young person CE10 Mum CE10	Male	8	9	31	Declined	Care outside RCT	CE

Family ID	Gender	Age	Socio-eco. (IMD decile)	Days between randomisation and interview	Status in trial	Treatment group	Site ID
Young person CE9 Mum CE9	Male	13	4	34	Declined	Care outside RCT	CE
Young person CF18 Mum CF18	Male	13	4	15	Declined	Care outside RCT	CF
Young person CF15 Mum CF15	Male	5	7	22	Declined	Care outside RCT	CF
Young person CF21 Mum CF21	Male	15	8	10	Declined	Care outside RCT	CF
Young person CD11 Dad CD11	Male	13	9	56	Declined	Care outside RCT	CD
Young person CD8 Mum CD8	Male	12	6	23	Declined	Care outside RCT	CD
Young person CD12 Mum CD12 Dad CD12	Female	11	1	24	Declined	Care outside RCT	CD
Young person CD4 Mum CD4 Dad CD4	Male	12	2	46	Declined	Care outside RCT	CD

Appendix 10: Lone working procedures

Appendix 2: FIELDWORK RISK ASSESSMENT FORM

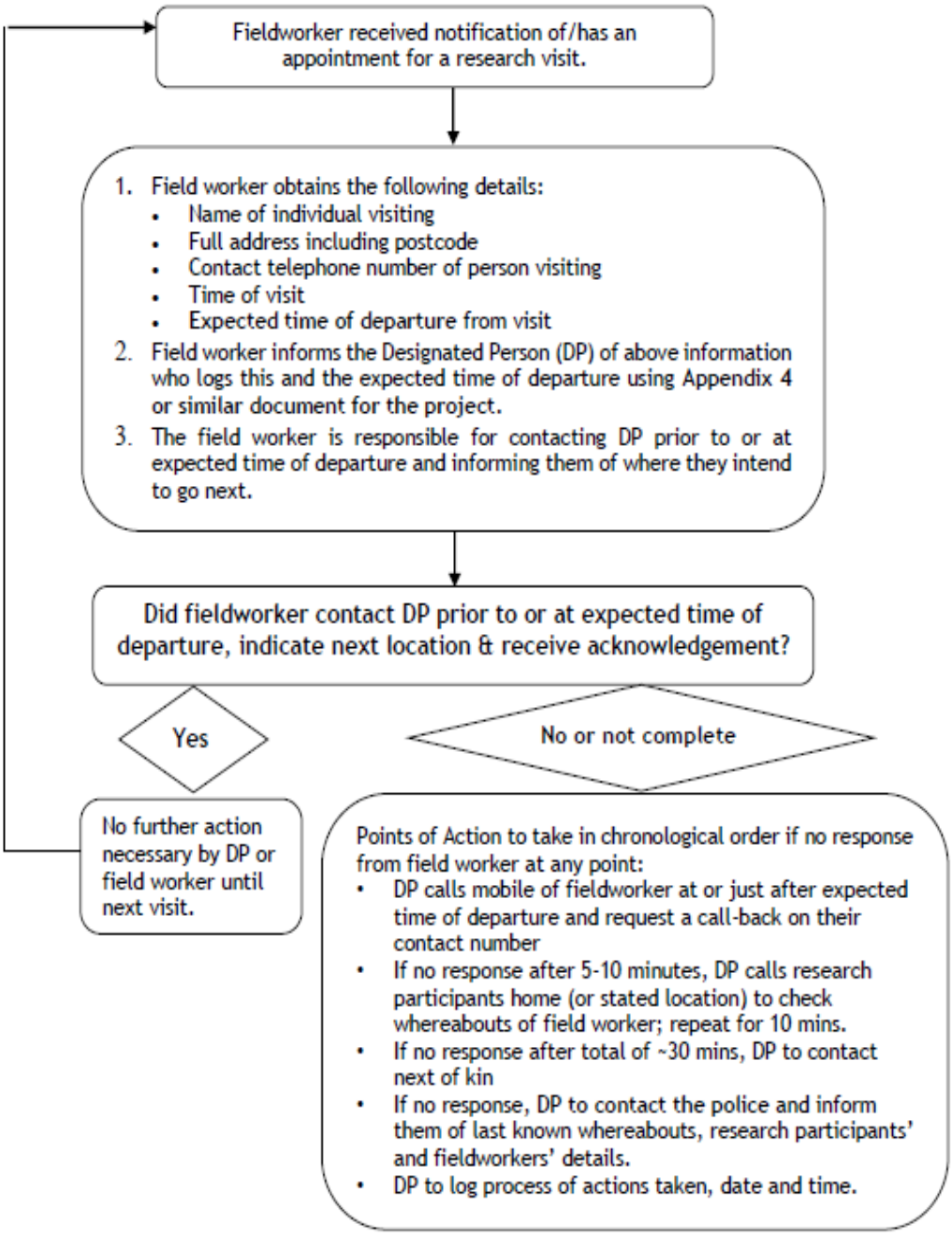
Name of Project and task		Name of line manager	Name of fieldworker	Project start-end dates
Risks	**Who might be harmed?**	**In what ways could the risks be managed/minimized?**	**What action is necessary?**	**Dates of action performed/review of risks**

Line manager's signature:..... **Field worker's signature**.....

Date: / /20 .

Standard operating procedure for designated persons supporting fieldworkers
(Appendix 3 in SOP)

Name of project:	
Name of field worker:	
Designated Persons (Normal working Hours):	
Designated Persons (Out of Office Hours):	



Appendix 4: VISIT RECORD

Please note: multiple double-sided copies of this form with the *first page* already completed for each field worker should be passed to DPs in advance of visits. This can be modified to the requirements of the project, but must be reviewed and agreed by the PI/manager.

Field worker details

Name		
Project name		
Safety phrases	I am in danger and need urgent assistance.	
	I am safe but having difficulty and require you to call the mobile number again in 10 minutes, and continue doing so until assured you of their safety.	
	I am fine.	
Office telephone number		
Work mobile number		
Personal mobile number		
Home telephone number		
Address		

Next of kin details (complete where different from above)

Name	
Office telephone number	
Work mobile number	
Personal mobile number	
Home telephone number	
Address	

Method of travel:

If car, then complete car details:

Make		Model	
Colour		Registration	

Visit details: research participant/premises information:

Name		Date of Visit	
Phone Number		Time of Visit	
Address			
Reason for Visit			

Security

	Time
Arrival Confirmed	

	Expected Departure Time
Duration	

	Revised Expected Departure Time (if appropriate)
Revised Duration	

	Time	Confirmed By
Departure Confirmed		

If no departure confirmed, please record action taken:

_____

_____

_____

_____

_____

Visit Record Complete..... **(DP signature)**

Please note: University Security Services 24-hour emergency number: **0117 331 1223** (internal **112233**); Control room 0117 928 7848 (internal 87848).

Appendix 5: EXAMPLE SAFETY PHRASES

Safety phrase	Meaning
CANCEL ALICE, I'M RUNNING TOO LATE NOW	I am in danger and need urgent assistance.
CAN YOU FIND OUT WHERE THE MEETING IS AND LET ME KNOW	I am safe but having difficulty with the visit and require you to call the mobile number again in 10 minutes, and continue doing so until the staff member has assured you of their safety.
I'LL CALL YOU BACK WHEN I LEAVE	I am fine.

Appendix 11: Transfer of digital recordings

STANDARD OPERATING PROCEDURE:

Transfer of digital recordings

1. INTRODUCTION, BACKGROUND & PURPOSE:

The purpose of the following SOP is to describe the procedure for downloading files from a digital device (Olympus DS-3400) to an NHS or University of Bristol PC (e.g., after recruitment/randomisation / interview discussion & intervention session).

2. ABBREVIATIONS

University of Bristol: UoB

3. SCOPE

All discussions about recruitment/randomisation, between family members and the recruiter will be routinely recorded and need to be transferred onto secure University of Bristol servers for analysis.

All interview discussions between family members and the qualitative researcher will be routinely recorded and need to be transferred onto secure University of Bristol servers for analysis.

All follow up intervention sessions for participants recruited to the trial will be routinely recorded for analysis by members of the clinical team delivering treatments and need to be transferred onto secure University of Bristol servers for analysis.

4. RESPONSIBILITIES

The recruiters, qualitative researchers, and members of the clinical teams delivering follow up sessions will be responsible for storing and transferring files holding identifiable patient information. The project co-ordinator & principal investigator, (PI) will be responsible for overseeing this process, ensuring that all staff are transferring audio-recordings in a timely and secure manner.

PI: *[Removed]* **Project Co-ordinator:***[Removed]* **Recruitment:** *[Removed]*

Qualitative discussion:*[Removed]* **Recording Clinical sessions:***[Removed]*

5. PROCEDURES

a. Load Olympus dictation software onto your PC if it's not already available, (see Olympus DS3400 Encryption Instructions manufacturer instructions).

b. Ensure the Olympus DS3400 digital recorder is fully encrypted with the following passwords: The machine pin for all is: **XXXX** Folders: **XXXXXX**

c. Click on 'Dictation Module' on the program start menu to access the Olympus DSS Pro Dictation Module OR connect the digital recorder to the PC via the lead and the dictation module should open automatically.

d. Attach the digital recorder to your PC (you will need to enter the encryption code to open the recorder: xxxx) to view recorded file & click into any of the 'device manager' folders with labelled A-E (see screen shot below – bottom left)
e. Select 'download all' to transfer your files from the device (folders in bottom left of screen) to folders in the dictation tray:
f. Right click on the relevant audio file and select – decrypt – input the decryption password (XXXXX)
g. Once decrypted copy and paste the file into your named folder on the shared data drive:Shared drive: Z:\sftp\uploads\xxxx\Audio Recordings\XXXX
h. File names cannot be changed on NHS computers so leave the file name assigned by the digital recorder and the research team will amend file names using the consent/research ID and date read out at the beginning of the recording.
i. As soon as the research team confirm receipt of the audio file & that they have checked that transfer has been successful (e.g., it is openable) the original audio file saved on the device can be deleted.

6. RELATED SOPS, WORK INSTRUCTIONS AND DOCUMENTS

Olympus DS3400 Encryption Instructions manufacturer instructions

SOP_Audio_Recording_FileTransfer

http://data.bris.ac.uk/sharing/collaboration/information-for-collaborators-webdav/

7. FORMS/TEMPLATES TO BE USED (if applicable) N/A

8. REFERENCES (if applicable) N/A

9. APPENDICES (if applicable) N/A

10. CONTACT LIST (if applicable) [Removed]

Appendix 12: Patient and Public Involvement (PPI)

SMILE

During the development phase of the SMILE trial, (prior to this PhD research project) PPI was used to inform the design of the RCT. Representatives from the Association of Young people with ME (AYME) read and suggested changes to the protocol, and provided feedback in relation to patient consent forms, information leaflets and the interview topic guide. Teenagers' views on trial involvement and the concept of equipoise were also discussed with healthy school students at a Social and community Medicine departmental Young Persons' Advisory Group (YPAG) meeting.

MAGENTA and FITNET-NHS

Prior to the MAGENTA RCT (2014) a YPAG of past and current patients who had experienced symptoms of CFS/ME was set-up by Professor Crawley at the University of Bristol. This advisory group advised and commented on various aspects of each RCT as they were developed and set-up. Points relevant to the current PhD project included; the acceptability of patient information leaflets, the interview topic guide, mode of interview (home, skype or telephone) and using an online consent/assent system. The CFS/ME YPAG met twice a year to discuss the MAGENTA and FITNET-NHS RCTs, advising on recruitment, RCT processes and further changes to patient information sheets, including advice about the inclusion of a statement highlighting that young people *may* not get better with any type of CFS/ME treatment. Members also wanted the research team to make it clearer that

young people would receive core specialist treatment about sleep and symptoms in both arms during the FITNTE-NHS RCT.

CONTRACT

Prior to the CONTRACT RCT a PPI work stream was formed, this included a parent co-investigator who contributed to drafting the grant proposal and was involved at several points throughout the research program. It also included a Study Specific Advisory Group, (SSAG) of children who had experienced acute uncomplicated appendicitis, children who had not, and parents. The SSAG provided feedback in relation to patient/parent information leaflets and the interview topic guide, the agenda and outcomes of the initial SSAG meeting are shown below.

Study Specific Advisory Group (SSAG) agenda

CONTRACT

CONservative TReatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

Attendees project team: [deleted]

Young people: [deleted]

Parents: [deleted]

1. Introductions and icebreaker (Erin and all)
    I. *Icebreaker: sorting hat questions*
2. Quick re-cap of last meeting (Erin)
3. Randomisation study: Participant information sheets and video to feedback (Erin)
    I. *Distribute printouts of information sheets as an FYI, ask if there are any major concerns or omissions, otherwise will plan to submit these versions to ethics*
    II. *Show video*
4. Qualitative research
    I. Short introduction (Bridget and Lucy)
        i. *Short verbal background to the qualitative component of the study, why we're doing it, what it aims to find out*
    II. Topic guide for discussions
        i. *In a whole group, go through topics included in the topic guide so far, specific questions to ask?*
        ii. *How can we make the interviews as young-person friendly as possible?*
        iii. *Can you suggest any techniques for making the interview more of a conversation as opposed to a formal interview?*
        iv. *Feedback questions: Are they comfortable with these questions? Is there something missing?*
    III. Information sheets
        i. *In separate groups (parents vs young people), read and go through information sheets. How is the language? What would they add or take out? Thoughts on young person booklet? Are they happy with the assent procedure we have planned?*
5. AOB
6. Conclusion/wrap up
    I. *Thank everyone for coming, reiterate contact details, sign for vouchers, reimburse expenses*

Study Specific Advisory Group (SSAG) outcomes: PIL & Interview topic guide

PIL

1. The group felt we were not getting across the important message of 'why' we were doing the trial, particularly in the 'Things you need to do' section, and we need to highlight the fact that we want feedback from participants about how we can make the study better.

   [We amended the PIL for young people to reflect this]

   'Why have I been asked to take part?'
   We are asking you because **your option about how we can make the study better is very important to us** & a doctor already discussed the main CONTRACT study with you or your family.

   'Things you need to know'
   We are interested in your views on how we can improve the CONTRACT study.

2. In the 'what will happen if I take part' section there were issues with the fact that we specify how long the conversation with the researcher will take; '30 minutes'. They felt this was unnecessary and should be removed.

   [We amended the PIL for young people to reflect this]

Interview topic guide

3. The group didn't like Q1, too abrupt and too soon in the conversation:
   Can you tell me a bit about what happened when you began to feel ill with your appendicitis?
   Preferred more general Introductions, get to know each other.
   'Normal conversation' questions; hobbies, what they've been doing lately, where I'm from, what I like doing. 'Ground rules' for conversation e.g., confidentiality, not discussed with clinical team.

   Perhaps use: **What did you think when you were first told about the CONTRACT research study?**
   Take into consideration the fact that they may not want to 'think back' to when they were very ill/scared, may not remember.