The TRECA study: TRials Engagement in Children and adolescents (NIHR HS&DR 14/21/21)

PROTOCOL

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1. Background

1.1 The clinical evidence base for children and adolescents

The effectiveness and safety of healthcare interventions is best determined by evidence from randomised controlled trials, but the absence of robust trials in some areas means that clinical decisions are being made without valid evidence. This is particularly the case in treatments for children and adolescents, for which there is often extrapolation from trials involving adults. In 2009, research involving children and adolescents comprised only 10% of all UK National Research Ethics Service applications, and less than 10% of those were pharmaceutical trials (i.e. CTIMPs) [1]. A systematic review of barriers to pharmacokinetic research in children found that high rates of patient refusal were very common [2].

Trials involving children and adolescents are often relatively small – a survey of 100 UK registered trials recruiting children and adolescents found that half had a target sample size of less than 300 [3]. The same survey also found that more than 80% of children and adolescents trials concerned long-term conditions. Trial sample sizes will have been determined by both the statistical power needed to test effectiveness and a target considered achievable given the incidence of a condition in children and adolescents. However the small size of trials emphasises the relative lack of evidence available to inform treatment decisions about children and adolescents. Both the Chief Medical Officer's recent report ('Our Children Deserve Better: Prevention Pays') and professional bodies stress the need to *"facilitate increased participation of children and adolescents in… trials"* [4 p9, 5]. This aspiration is echoed by the NIHR, which has recently funded significant amounts of research to provide: *"…the evidence base to improve outcomes for children and adolescents that result from long-term conditions."*

1.2 Recruitment and retention in clinical trials

Major barriers to the successful conduct and outcome of clinical trials are levels of recruitment and retention. In the UK only a small proportion of trials recruit successfully to time and target [6, 7]. Furthermore, most patients are not recruited to trials; it remains relatively uncommon for a patient to take part in a trial. This has implications not only for conclusive results; it also questions the notion that a trial has external validity and generalizability. Such concerns underpin the 'Research Active Nation' initiative of NIHR [8], stressing the role that 'citizens' can play in research, which could lead to *"…best health for all through high quality research".*

The acceptance of the trial as the core source of knowledge on intervention effectiveness has led to a large growth in the number being conducted and reported in the last 20 years. Given the continuing problems of trial recruitment and retention, it is surprising (and ironic) that so little work has focussed on developing an evidence base to inform recruitment and retention. The Cochrane systematic reviews on trial recruitment and retention [9, 10] are regularly updated but continue to show a lack of evidence in some promising areas for interventions. This is particularly the case for children and adolescents: the current review on retention in trials contains 38 trials, none of which included children and adolescents patients; the current recruitment review includes one trial of children and adolescents from a total sample of 45 trials.

1.3 Information for potential trial participants

A potential barrier to recruitment and retention relates to the information provided to potential trial participants. Conventionally it is written and in printed form. However it has received recurrent criticism, notably for being too long, difficult and technical, impacting most on those who have lower levels of education and/or are less able readers [11, 12]. Other qualities of good information design are often lacking, such as a structure to help navigation, and visual appeal to invite and engage the reader. Furthermore, the content of trial sheets is mostly guided by regulatory agencies and can be inconsistent with what patients want to know [13], and its overall purpose may be unclear. For

example, written information should inform a decision about participation, but may act more as a prospectus for the trial and as a contract between researchers and the participant [14]. However studies that we have undertaken show that re-writing, re-designing and user testing of trial information can produce an understandable and preferred resource [15-17].

Making changes to the information available to potential trial participants may impact on behaviour (i.e. recruitment, retention and intervention fidelity) and cognitions (i.e. the quality of decision-making on participation; evaluations of the trial). In children and adolescents patients the evidence base is almost non-existent, although our work in adult patients shows that optimising written information can affect outcomes [18].

1.4 Multimedia information

Audio-visual information about trials may be an alternative or adjunct to printed information and have been evaluated in a few studies, but no studies involved children and adolescents or their parents [19]. Overall audio-visual presentation showed a small increase in patient understanding but no effect on rates of trial recruitment.

By comparison multimedia information resources (MMIs) containing information in different formats (i.e. textual, audio and video) may impact on patients' understanding and engagement, with potential effects on decision-making. This may be due to a number of factors, including the way that the range of available media (reading, listening, watching) allows patients with different preferences to use the resource effectively. Furthermore MMIs allow the patient to select the order in which they access the information, which is less easy with a printed or video resource. Finally people's familiarity with websites and the frequency of their use, means that MMIs presented on a computer (or smartphone) may now be used intuitively and easily by most people.

Two systematic reviews reported that informational MMIs about medical procedures improved patient knowledge, but none of the included trials involved children and adolescents [20, 21]. However a recent trial of children and adolescents undergoing endoscopy showed that electronic presentation of information produced more certain consent decisions, by comparison with printed information [22]. A recent systematic review of interventions aimed at improving informed consent included 13 trials that tested video or computer presentation of information [23]. Some showed improved understanding compared with printed materials and others showed no difference. However the tested video / computer interventions were mostly quite rudimentary, being neither multimedia nor interactive. For example in one case the information sheet was presented in text form on a screen for the patient to scroll; in another Powerpoint slides and a recorded audio commentary summarised the trial. Only two of the 13 trials recruited parents of children and adolescents patients, who in both cases decided about a hypothetical trial. This suggests scope for an intervention for children and adolescents and/or parents that is both multimedia and interactive, and for testing its effect in real trials. Such interventions may not only inform but also increase children and adolescents' and parental engagement with the trial and provide the required "scaffolding" for communication with clinicians [24]. This may also help parents when making decisions about their child - a recent systematic review reported that, when making health decisions about a child, parents ideally need information and communication with other parents (or testimonials from them) [25]. A further consideration is tailoring to the patient group – the beneficial effects of MMIs may depend on it – and their being tested before implementation [26].

1.5 Access to the internet and 'media literacy' among children and adolescents

Arguably the success of an MMI to inform children and adolescents about trial participation would be dependent on access to the required technology and familiarity with the MMI format. MMIs can resemble a website and while internet access among children and adolescents in the UK is not universal, it is nearly so. In 2013 Office for National Statistics (ONS) data showed that 73% British adults accessed the internet daily, compared with 41% in 2006 [27]. Access rates in those aged 16-24

were higher than in any other age band, a finding also reported by Ofcom [28]. No ONS data were available for under 16s but a small survey of 12-18 year olds in 2012 reported that 66% owned a smartphone capable of internet access [29], with the authors claiming that current teens are the most "connected generation", seen to have high levels of 'functional literacy' about the internet [30]. A recent European study [31] suggests nearly a third of 9-10 year olds and over 80% of 15-16 year olds can access the internet on a personal mobile device.

The 2013 ONS survey also reported that more than 80% British households had internet access, rising to 97% in households with children. Among households without internet access, 25% cited equipment or access costs [27]. Income and social class can be barriers to children's internet use, not only in owning equipment and having access, but also in the way that parents with higher levels of education are able to offer children more guidance on web usage [30]. Overall there appears to be a small 'digital divide' among children and adolescents in the UK, based predominantly on household income and parental education.

1.6 Multimedia information resources (MMIs) in embedded trials

Although there is little evidence on the use of MMIs in informing children and adolescents about trial participation, this study builds on work that members of the research team have done in testing MMIs to recruit to adult research. However qualitative work with key stakeholder groups (principal investigators, research managers, research ethics committee chairs and funding body representatives) highlighted key challenges to embedded studies [32]. Although respondents recognised the case for embedded studies, enthusiasm was tempered by implementation challenges. Perceived challenges for host trials included increasing complexity and management burden; compatibility between host and embedded trials; and the impact of the embedded study on host trial design and relationships with collaborators. For embedded recruitment studies, there were concerns that host trial investigators might have strong preferences, limiting the embedded study investigators' control over their research. Overall, research on recruitment was welcomed in principle, but raised issues over control and responsibility. To address this concern, it was seen as important to align the interests of both host and embedded trials.

These findings informed the MRC-funded START collaboration [33] which members of the TRECA study team have led. START is testing the development and use of MMIs in six adult trials and has produced useful knowledge on drafting a specification for an MMI; how to incorporate both generic and study-specific information; the role of infographics, text and video; design for use on multiple digital platforms; and the importance of lay contributions to MMI design.

1.7 Participatory design and user testing in the development of MMIs

One approach to information development is participatory design, in which small numbers of end users are closely involved. This would be consistent with the Chief Medical Officer's view that researchers *"…should work with children and adolescents to input to the design of clinical studies…to facilitate (their) increased participation in trials."* [4]. Participatory design may take a number of forms, including 'participation via proxy' when the needs of children would be represented by people with detailed knowledge and expertise, such as teachers, paediatric staff or educational experts. By contrast a 'full participation' approach allows end users to have direct impact on the process and outcome. At its best Participatory Design has many benefits [34], including a better understanding of user requirements. When a Participatory Design approach is used, consideration is needed to the method, tools and techniques [35] as well as the role that end users play in decisions.

Two potential components of participatory design are the involvement of potential end-users in defining the format and content of the object, and user testing, in which an information resource is tested for its function or performance; i.e. its ability to inform its audience. This contrasts with a checklist or content-based approach to evaluation, such as readability formulae [e.g. 36] or quality

measures [37]. Performance-based methods are likely to provide a more valid indicator of the information's functioning (whether printed, audio, video or multi-media) [e.g. 15, 38].

1.9 Law and guidance relevant to research in children and adolescents

Research involving children and adolescents in the UK is governed by law and by guidance from the Health Research Authority (HRA) [39]. From the age of 16, a person can consent to all forms of health research including CTIMPs. Under 16, CTIMP participation requires consent from a parent or guardian; for other research different rules apply. In England, Wales and Northern Ireland consent for research (including trials of interventions other than pharmaceuticals) can be taken from a child aged under 16 if s/he is judged competent, applying the 'Gillick competencies' rule that applies to treatment consent [40]. That is, *"…sufficient understanding and intelligence to understand fully what is proposed, and can use and weigh this information in reaching a decision"* [39]. In Scotland there is similar competency-based guidance*: "…dependent upon (children and adolescents) capacity to understand the specific circumstances and details of the research being proposed, which in turn will relate to the complexity of the research itself."* [39]

Both sets of guidance emphasise a need to involve children and adolescents in decisions on research participation and the crucial role played by information. There is particular emphasis when children and adolescents are not able to give consent but may be asked for assent: *"it is important that…you give the child / young person information about your study, which is understandable to them and which explains what is involved and the potential risks and benefits"*. 'Competence' for a decision is assessed individually, based on development and ability to understand, rather than age. However the guidance does mention some age expectations: Scottish law indicates 12 as a normal age threshold for involvement in research decisions; the HRA cites common law in guidance that people aged 16 would normally be competent to consent to non-CTIMP research; HRA guidance also states that children aged under 5 would not normally be asked for assent. Overall the varying roles of parents, and of children and adolescents giving consent or assent, suggest the need for information that can be adapted to the specific trial, the developmental maturity of the child or young person, and the individual family's approach to decision-making.

1.8 Assessing the MMIs: Embedded trials (aka nested trials)

The MMIs will be assessed using embedded trials. Methodological aspects of a trial, for example a recruitment intervention, can themselves be subjected to trial evaluation, with the methodological comparison 'embedded' within a 'host' healthcare trial [32]. Where possible, the results of several similar embedded trials can then be combined statistically in meta-analysis. Trial meta-analysis is most often undertaken retrospectively following a systematic review of the primary evidence, although it can also be undertaken prospectively (i.e. in a pre-planned way). Both forms of meta-analysis result in more certain estimates of effectiveness than individual trials can provide, and may also indicate the influence on effectiveness of factors such as the condition, age of patient, etc.

1.10 Summary

In summary, there is great potential for the use of informational MMIs when recruiting children and adolescents to healthcare trials, particularly if they have first been developed and tested carefully with prospective users.

2. Research gap

Many healthcare decisions made about children and adolescents are made without trial evidence and less than 5% of registered UK studies involve children and adolescents [1], with high rates of patient or parent refusal a key barrier [2].

When parental proxy consent is needed, the perceived consent threshold tends to be higher than for parents themselves [41]; parents and clinicians tend to opt for standard care and not a trial [5]. When

parents make child health decisions, ideally they need: information, communication with other parents (or testimonials) and decision making control [25]. Parents also need to be actively involved to ensure their concerns are covered [42]. The ethos and feel of decision making are important influences on its success [43]. The MMIs being developed in TRECA will ensure that information is given that is accessible to both parents and young people thus allowing for more informed decision making and discussion between parties regarding the trial participation decision.

Furthermore Cochrane systematic reviews on recruitment and retention in trials [9, 10] indicate a real lack of evidence for children and adolescents' involvement in trials: the embedded trials in TRECA will add significantly as detailed information about recruitment and retention will be recorded.

Finally, written trial information has received prolonged criticism [15, 38]. Trials of interactive MMIs show potential for improving recruitment [33] and MMIs for children and adolescents in healthcare settings can increase engagement and provide the required 'scaffolding' for communication with clinicians [24]. MMIs for medical procedures can improve patient knowledge but no trials have involved children and adolescents [20, 21]. The widespread use of the internet and smartphones suggest levels of familiarity and comfort that should allow young patients to make successful use of an MMI. Indeed, among children and adolescents there may be a preference for receiving information in this format. However, MMIs in healthcare perform better when tailored to the patient group and tested [26], both of which will happen in TRECA.

3. TRECA aims and objectives

The immediate aims of TRECA are to evaluate the potential for MMIs to improve the quality of decision making about participation in healthcare trials involving children and adolescents, and to assess the impact on trial recruitment and retention.

The long-term aim of the project is to increase the available clinical evidence base for the treatment of children and adolescents, including those with long-term health conditions.

The objectives are:

1. To involve children and adolescents with long-term conditions (and their parents and clinicians) in the development of two MMIs, for use when children and adolescents are being asked to consider healthcare trial participation.

2. To obtain and analyse qualitative data from focus groups with members of key stakeholder groups (i.e. young patients with long-term conditions; parents; clinicians; triallists; regulators who will stipulate requirements) to ensure that the content and format of the MMIs reflect their preferences.

3. To user test the MMIs with children and adolescents (and their parents), to test the ability of the MMIs to inform potential users.

4. To evaluate the MMIs in a series of trials embedded within healthcare trials, and test their effects on recruitment and retention rates, and decision-making, by comparing the effects of providing standard written participant information with provision of the MMIs either in addition to the standard written participant information or the provision of the MMIs alone.

4. Research plan

The study is divided into two phases: Phase 1 (development) and Phase 2 (evaluation).

The development phase includes qualitative methods (study 1) followed by user testing (study 2), aiming to produce two MMIs, with generic elements relevant to any trial involving children and adolescents and a template for the addition of specific content for individual host trials. In the evaluation phase, the two MMIs will be tested in a series of embedded trials hosted within healthcare trials, following the addition of a small amount of content to the MMI specific to that host trial. The MMIs will be tested for their impact on cognitions (i.e. decisions about trial participation taken by children and adolescents and/or parents) and behaviours (rates of recruitment to, and retention in, the host trials).

- Phase 1 features two studies and draws on several theoretical and conceptual frameworks. The overriding influences on Phase 1 are of participatory design and information design; that is, first, involving potential users of an intervention in the development of its content, style and delivery, and second, using evidence and good practice to develop information that is inviting, engaging and which works to inform.

- The Phase 2 evaluation of the MMIs is based on the premise that individuals' decisions in healthcare are influenced by a number of factors, and that some influential factors can be isolated, manipulated and tested for their effects on outcomes, by using a trial design.

5. Phase 1 (MMI Development; months 1-10)

In Phase 1 we will involve children and adolescents with long-term conditions (and their parents and clinicians) in the development of two MMIs for use when children and adolescents are being asked to consider clinical trial participation. Phase 1 comprises two studies: Study 1 (qualitative methods) and Study 2 (user testing).

6. Phase 1, Study 1: Qualitative study

In Study 1 we will obtain and analyse qualitative data from focus groups with members of key stakeholder groups (i.e. young patients with long-term conditions; parents; clinicians) on their preferences for the content and format of the MMIs, then adapt the MMIs accordingly.

Study one in Phase 1 is qualitative - i.e. both inductive and interpretive, and analysis will be informed by the Framework approach [44], intended to develop a thematic analysis of spoken data derived from focus groups. Focus groups have been chosen in preference to individual interviews, given their potential to stimulate discussion. However individual interviews – either in person or remotely (via Skype / Facetime for example) will be conducted if a participant is unable to travel. We intend to conduct two rounds of data collection; the first before any design work has been undertaken on the MMIs (i.e. to inform their content, style and delivery); the second to hear participants' reactions to the draft MMIs and their ideas for amendments.

6.1 Sampling and entry criteria

Data will be collected in focus discussion groups and we plan to conduct two rounds of 5 groups, each group comprising around 8 (6-10) participants, although we will increase the number of groups, if required, based on principles of saturation. The five groups will comprise different 'stakeholder' groups in relation to this issue:

Groups A, B and C: children and adolescents with long-term conditions, divided into three groups by age: 9-11 years, 12-14 years and 15-17 years. The age split is based approximately on children's likely role in consent decisions.

Group D: parents of children and adolescents with long-term conditions.

Group E: clinicians (mostly doctors and nurses) and researchers, all with experience of recruiting children and adolescents into research.

Recruitment of focus group participants will be via a number of mechanisms. Clinicians and researchers will be recruited from Alder Hey Children's Hospital. Young people and parents will be recruited through a number of patient interest groups: Generation R Young Person Advisory Groups (located in Liverpool, Nottingham, Birmingham, London and Bristol), the Paediatric Oncology Reference Team (PORT), the UK Juvenile-onset Systemic Lupus Erythematosus (JSLE) Study Group and the Invisible Illness group run at Alder Hey Children's Hospital. Young people and their parents who are attending Alder Hey Children's Hospital for a trial appointment will also be approached to participate in the focus groups.

Sampling will be purposive, not only according to the 'stakeholder' group criteria, but also aiming to achieve maximal variation on other factors anticipated to influence stakeholder views, including gender; job type (re clinicians and researchers), postcode (as a proxy for socio-economic status), long-term condition [45], trial experience and type of site (recruiting not only via bigger, research-intensive centres but also smaller, district hospitals). Where possible we will also aim for ethnic diversity in the groups. However, we acknowledge that group sample sizes are small and the aim is to attain sample variation, not population representativeness.

If possible the two rounds of focus groups will use the same participants to facilitate respondent validation of the ongoing analysis, with some replacement for the second round, when required. Ideally the groups will include some children and adolescents who are newly diagnosed, to ensure that MMI development is informed by a range of participants and not only those with many years' experience of living with the health condition.

6.2 Data collection

Group discussion will draw upon topic guides, developed with input from the patient and public Involvement (PPI) groups (see section 14), and they will be facilitated by a researcher and two adolescents (or parents) from the TRECA PPI group. In the first round of groups, discussion will focus on i) preferences for information about research and, ii) preferences for content, style and delivery of the MMI. For the former, participants will be asked to discuss the importance of a list of statements adapted from Kirkby et al 2012 [46] about important information to be given to trial participants. This includes factors such as:

- Why the study is being done;
- Whether they have to take part or not;
- Whether they will benefit from taking part; and
- Who will know they are taking part.

For the latter, participants will discuss the importance of factors related to how the MMI looks and functions. These are based on the criteria used in the website industry Webby Awards [47] and include factors relating to:

- General preferences for MMI content;
- Potential for interactivity (e.g. question posting, quizzes); and
- What the information looks like.

Stimulus material will include information examples related to recruitment to previous trials, e.g. video and written trial information, and relevant text from UK Health Research Authority guidance.

In the second round of focus groups, held 2-3 months later, the discussion will focus on two draft MMIs, used as stimulus material, with discussion centred on MMI content, style, tone, delivery

including opinions regarding the differences in style and content between the two MMIs and the ease of distinguishing between trial generic and trial-specific content.

Each group will last no longer than 90 minutes, potentially shorter for groups involving younger children. The group discussions will be audio-recorded and transcribed verbatim, to facilitate data analysis.

A group of children aged 6-8 will be asked to review the MMIs during the second round of qualitative data collection, as a pilot study to see whether children of this age can use the MMI and are able to provide feedback.

6.3 Data analysis

The primary purpose of the analysis is the development of the MMIs, based on the preferences and attitudes of potential users. The analysis, which will be led by study researcher Dr Jackie Martin-Kerry and guided by co-investigator Professor Bridget Young, will draw upon the Framework approach and place particular emphasis on preferences for information content and delivery, and the context in which participants anticipate using the MMIs. We will explore the MMIs' functions from participants' perspectives, including reasons for preferences for topic inclusion and omission. Analysis will also report consensus and dissent within groups and between groups to look for, and take account of, the different perspectives of clinicians and researchers, children and adolescents and parents on MMIs for making informed decisions about trial participation.

Following the second round of focus groups, the MMIs will be revised, where appropriate. At the end of the qualitative study in Phase 1, we will have developed two MMIs containing content applicable to all trials recruiting children and adolescents and a template for adding trial-specific content.

6.4 Multimedia information resources (MMIs)

Within TRECA the MMIs are the novel intervention under evaluation. We will develop two MMIs to inform patient (and parent) decision-making about host trial participation. The MMIs will be commissioned from a specialist commercial supplier following competitive tender, so that their appearance and function are professional, sophisticated and contemporary. Copyright will not be assigned to the MMI supplier. In developing the MMIs, we will draw upon our experience of developing MMIs for adult patients in the MRC START project.

The MMIs will feature some topics generic to all trials (e.g. uncertainty, randomisation, altruism and personal benefit, withdrawal, confidentiality, follow-up, provision of summary of findings to participants), and some topics specific to the host trial (e.g. the trial's questions, interventions, any additional patient appointments, length of follow-up). The MMIs will feature text, infographics (that is, static or animated representations of concepts), and short video clips explaining trial relevant information in a different format . The video clips developed will be trial specific and may include, for example, the lead researcher explaining the trial's main questions. Content may also include video clips of children, adolescents and parents involved in the trial, or a similar trial, in some capacity. Including people who have some experience of trials in the videos will ensure their authenticity. Further, hearing information from other trial participants may provide reassurance to potential trial participants. This method of MMI development will be used for all Phase 2 host trials. We will also consider the potential for the MMIs to be interactive, for example, allowing children and adolescents to post questions to the host trial research team, and quizzes.

The two MMIs are intended for use by parents and children and adolescents of different developmental stages. The distinction between the MMIs will be informed by the Phase 1 qualitative study but we anticipate that the MMI for use by younger children will be smaller and less complex. The qualitative and user testing data will also inform whether all topics should be included in both MMIs, and the mixture of media (text, video and infographics).

The MMIs will be playable on a variety of platforms, including PC, laptop, tablet computer and smartphone. This means that a child, adolescent or parent could use the MMI in the hospital clinic on a tablet computer and then use it again at home on a smartphone or PC via a provided link.

7. Phase 1, Study 2: User testing study

User testing is an established, performance-based approach to testing information [38]. In TRECA, we will use the user testing method employed successfully in the development of printed information, including participant information sheets for trials [15] – i.e. an iterative process with changes being made to the information in response to obtained data. We anticipate having two rounds of user testing, with changes made to the MMIs, as required, after the first round.

User testing uses small participant samples to generate quantitative data, in which data patterns are interpreted to identify any problems with a piece of information that may be responsive to change. The generated quantitative data are indicative, not definitive, and not analysed statistically. Rather the emphasis is on identifying aspects of the information resource that might hinder understanding, explaining its alternative name 'information diagnostic testing'.

The user testing study will test the two MMIs for their ability to inform users; emphasising that in user testing it is the information resources and not the users who are being evaluated.

7.1 Participants

We will use the conventional sampling method in user testing – rounds of 20 participants (10 children /adolescents and 10 parents). As there are two MMIs being tested per round, the total sample size for both rounds will be 80 participants (40 for MMI 1, and 40 for MMI 2). For each round of user testing, MMI 1 will be user tested by 10 children aged between 6 and 11 years with their parent/guardian. For MMI 2, participants will include children and adolescents aged between 12 and 17 years and parents. For MMI 2, parents and young people will take part separately in order to acknowledge the increasing independence of young people with age.

As user testing is an iterative process, we will be flexible in the number of participants included in each round of testing. If there are no problems with the MMIs, user testing will be capped at 10 participants per MMI per round. If there are significant problems which require editing, user testing will be capped at 5 participants as this is a large enough number to demonstrate a general problem which is not just due to one person's interpretation of the MMI, but small enough to avoid wasting participant time by asking them to user test a suboptimal MMI. If significant issues are identified, we will conduct additional rounds of user testing until saturation is reached.

7.2 Sampling

Children and adolescents

For each MMI we will purposively sample children and adolescents to ensure variation in age, sex, sociodemographic factors and educational ability. For the older children and adolescents, we will also include a proportion of participants with English as a second language. To achieve this we will aim to sample from a school which serves an area with a range of socioeconomic statuses and where some children have English as a second language. If participants are recruited via schools, we will select participants in collaboration with class teachers in order to ensure our sample has children of differing educational abilities, sociodemographic factors and English as a second language.

Parents

For the parent participants needed for testing MMI 2, we will sample with variation in sex, socio-demographic indicators and English as a first language.

Finally, we will ensure that the participants in Round 2 of user testing have similar demographic profiles, to better indicate problems in the MMIs requiring change.

7.3 Inclusion and exclusion criteria

To be eligible to participate in the user testing, participants must not have any prior trial experience. This is due to user testing producing its most valid and insightful data when participants are potential information users but without significant relevant prior knowledge or experience [1]. For similar reasons we will ensure that the user testing participants are not those who took part in the focus groups (Phase 1, Study 1), as they have provided input into the design of the MMI and therefore have prior knowledge of the MMI.

We will include participants with long-term health conditions, though we will note if the participant has any experience with the health condition explained within the MMI (diabetes). Participants with diabetes will not be eligible to take part.

Additionally, we will ensure that those who take part in Round 2 of user testing did not take part in Round 1, to remove any effect of prior learning.

7.4 Recruitment

We will aim to recruit child and adolescent participants through primary and secondary schools in England. Initial contact will be made with the relevant staff of potential schools (e.g. headteachers, senior management team, school liason officers) to inform them about the study. If the school staff would like to take part, a senior member of staff will confirm the school's participation and ask their staff to recommend children who fit our study criteria. Children and adolescents who are eligible will be contacted with an age-appropriate information pack which will be sent via the pupil's school. This will include a letter of support from the school, a participant information sheet and an assent/consent form.

For MMI 2, we will aim to recruit the parents of the children and adolescents who take part in the user testing of MMI 2 through the expression of interest form included in their child's recruitment pack; we will widen recruitment to parents in the rest of the school if there is little interest. Potential parent participants will be sent a recruitment pack once again including a letter of support from the head teacher, a participant information sheet and a consent form to be returned to their child's class teacher.

If we struggle to recruit participants via local schools, we will then recruit via Young Person's Advisory Groups, the Birmingham Children's Hospital Rare Disease Team, local Charities and through colleagues in the Department of Health Sciences, University of York.

7.5 Data collection

Before testing begins, the researcher will talk to the participant in order to develop a rapport and make them feel comfortable before user testing. User testing interviews for children, adolescents and parents will be conducted in a quiet room with a TRECA researcher trained in user testing. We will be flexible with the location and timing of user testing interviews. For MMI 2 the sessions may take place during the school day; this may not be possible for MMI 1 due to the child's parent needing to be present. If testing takes place outside of the school day, we anticipate that it will take place in a local meeting space. Participants will be settled in front of the MMI and informed again about what the study involves, reminded that discussions will be audio-recorded and will then be asked to provide verbal assent/consent before testing begins. It will be emphasised that we are testing the usability of the MMIs, and not the performance of the participant.

The participant will be given a maximum of 10 minutes to interact with the MMI to familiarise themselves with its structure and layout, and to play video, read text, etc, as they prefer. The

interviewer will record the amount of time the participant spent looking at the MMI. The interviewer will then use a structured questionnaire containing questions for which the required factual answer can be found within the MMI. The questions will not relate to sequential information in the MMI. In response to each question, the participant will be asked to find where the answer is located, and then verbally provide the answer (using their own words when possible). These two aspects of the question will test, first, the structure of the MMI and the ease of navigation, and secondly, the ability of the MMI to inform. If participants appear to be struggling with finding or explaining the information, the researcher will repeat the question to them and prompt them gently for an answer. For any words or phrases within the MMI that may be complex for healthy participants (e.g. subcutaneous insulin), participants will be given a card displaying the word to assist them with the finding of relevant information.

After the structured questions, participants will then be asked for their general opinions (open-ended questions) about the MMI.

For the testing of both MMIs we will ensure that the question wording and number of questions are age-appropriate. The length of user testing interviews can vary according to participants' speed of finding and understanding answers; however, we expect that interviews with children and adolescents will last roughly an hour.

Pilot Interviews

We will run one or two pilot user testing interviews before Round 1 of testing in order to check question wording and interview length. We will ask members of the TRECA Patient and Parent Advisory Group to be the interviewees for these pilot interviews.

7.6 Data analysis

Each item on the questionnaire will derive the following scoring criteria:

Finding

- Found
    - Participant was able to correctly show where on the MMI they found the information.
- Found with difficulty
    - Took the participant over 2 minutes and 2 seconds to respond
    - Participant asked for question rewording/repetition 3 times within 2 minutes
    - Participant was prompted 3 times within 2 minutes.
- Not found
    - Participant was unable to find the relevant information within the time limit (3 minutes depending on MMI difficulty/length)
    - Participant was unable to find the relevant information and wanted to move on.

Understanding

- Understood
    - Participant was able to provide the correct information.
- Understood with difficulty
    - Took the participant over 2 minutes and 2 seconds to respond
    - Participant asked for question rewording/repetition 3 times within 2 minutes
    - Participant was prompted 3 times within 2 minutes.
- Not understood
    - Participant was unable to give provide the correct information within the time limit (3 minutes depending on MMI difficulty/length)
    - Participant was unable to provide the relevant information and wanted to move on.

The researcher will record which criteria the participant met for each question, and will also write down any behavioural observations which may further inform MMI design e.g. a participant struggling to find a particular topic heading. Each interview will also be audio-recorded meaning the researcher can re-assess participant interviews and resolve any uncertainties with colleagues.

The data derived from user testing interviews will be analysed quantitatively, although data are merely indicative, not probabilistic. The data will be summarised and assessed by pattern spotting, i.e. identifying aspects of the MMI that are causing problems of finding or interpreting information in more than one of the 20 participants. Consistent with previous studies, we will determine whether 80 per cent of participants could find and understand the information and how many participants could answer all questions adequately. Following data analysis of Round 1 of user testing, the MMI(s) will be revised as required before Round 2 of user testing begins. Further changes to the MMIs will be made, as required, after Round 2.

8. Phase 2 (MMI Evaluation)

The MMIs for the host trials will include a mixture of text, diagrams, animations and video that will cover generic trial content plus host trial-specific content (as described in section 6.4). These MMIs will be developed using the host trial PIS document(s). Video clips will be developed by interviewing clinicians, children, adolescents and parents involved in either the host trial or a similar trial. They will cover aspects such as trial procedures, how to stop taking part in the study and what happens when the study ends.

The effectiveness of the two MMIs will be evaluated in a series of embedded trials, set within host healthcare trials, recruiting children and adolescents. The objective is to test the effects of the MMIs on cognitions and behaviours: (a) whether individuals who see the MMI(s) make a more informed decision about trial participation (or not); (b) whether rates of recruitment to the host trials are increased; (c) whether rates of retention in the host trials are increased; and (d) whether they are more satisfied with the process of consent or assent. As well as assessing the impact in any one host trial, the data from the nested trials in each age group will be combined statistically within a prospective meta-analysis, to assess the effectiveness of the MMI interventions across a series of similar trials.

8.1 Design

The evaluation phase will use an embedded randomised controlled trial design, with potential participants in the host healthcare trial receiving one of three versions of the recruitment information. Outcome data will include subjective and objective measures. The results of the individual trials will be combined statistically in a prospective meta-analysis.

Each of the embedded trials will normally use a three arm design, in which individuals will receive either the standard written trial participant information sheet (PIS) alone, the standard PIS in addition to the MMI (or MMIs) or the MMI(s) only. For those who receive both the MMI and the PIS, we will consider making the written PIS available via the MMI – for example, by a link to a Word or pdf document from within the MMI. This would have the advantage of being more efficient, allowing people to access both the MMI and the PIS via the computer. However we will need to consider important practical concerns such as text readability on screens and participant preferences, and so will seek the opinions of participants in the focus groups during the development study phase.

In the embedded trials allocation to groups will be achieved by random number generator or another randomisation method that suits the practicalities of the host trial. Trials will use individual or cluster randomisation as deemed practical and appropriate. For those trials who use cluster randomisation, we will use only two arms of TRECA (PIS only versus MMI only) to enable the power to be increased and the impact of the MMIs to be more robustly evaluated. We will aim to achieve concealment of allocation, with decisions about whether a child or adolescent patient will receive the MMI or not

(either alone or in addition to the PIS), being communicated to the clinician / researcher only after the patient has been recorded as recruited in the nested trial. Masking of the allocation at outcome measurement is not possible but also irrelevant: the patient cannot be masked to the information format s/he will receive but, as s/he will be unaware of the embedded information trial, a lack of masking will not affect his/her responses on the self-completion measures, or have any biasing effect on their decisions on trial participation or continuation. Furthermore, it seems highly unlikely that the decisions taken by children and adolescent patients on recruitment to, and retention in the host trial would be influenced by the lack of masking among clinicians or researchers.

We will report the conduct of the embedded trial in line with reporting guidelines under development in the MRC START project (led by Professor Eldridge, QMUL).

8.2 Sampling and entry criteria

Trials will be eligible for inclusion in TRECA if they are testing an intervention being given to children and adolescents. Within each embedded trial participants will be children and adolescents and/or parents being asked to participate in the host healthcare trial. This is critical, as it means that the host trial and the embedded trial have different sample sizes. For the host trial the sample comprises those children and adolescents/parents agreeing to participate; for the embedded trial the sample comprises those asked to participate. In some trials the number asked to participate is a much larger number, often more than double the host trial sample size.

Selection criteria for the inclusion of trials in TRECA will include:

- having sufficient sample size to detect a difference between groups in the embedded trial;
- using only printed or video participant information materials as standard (i.e. not already including an MMI);
- recruiting at least some children and adolescents who have potential to contribute to a decision about consent (or assent) to trial participation. This means that trials will not be included if they are only recruiting children too young to understand an MMI, or children with intellectual impairment such that understanding or use of the MMI is not possible.

Trial inclusion in the study will be determined primarily by the potential of the planned MMIs to improve the quality of decision making among potential participants. However, if a choice is possible, we will also opt for trials that are anticipating lower rates of recruitment and/or retention. When possible we will also aim to recruit larger trials, and those recruiting at more than one centre, to increase both the statistical power and the generalizability of the study. It will also be possible to recruit host trials for which participant recruitment is already underway; in other words, introducing the nested trial during just one period of the overall recruitment period.

It will be possible to undertake embedded trials of the MMIs using host trials that are recruiting through single- or multiple-centres; however if we recruit multi-centre trials we may run the embedded MMI trial in a limited number of centres, to ensure the study is achievable. Among trials that meet these criteria we will aim to vary the following features:

- condition (using PRISM study criteria);
- age of children and adolescents being recruited;
- host clinical trials unit;
- type of intervention (e.g. pharmaceutical; physical therapy; psychological or educational)
- the way that the MMI will be presented to patients.

It is likely that there will be variation among the six embedded trials in the MMIs used, depending on the age of children and adolescents being recruited. In trials recruiting children and adolescents across a narrow age range, only one MMI might be used. In others, there will more variety, including

the following situations: i) parental decision only; ii) adolescent decision only; iii) parent and children and adolescents both using the larger, more complex MMI; and iv) parent using one MMI and a younger child using the other, smaller MMI.

In some host trials all four situations may apply. In these circumstances, indeed in all the embedded trials, the decision about who uses the MMI (and which version) will be left to the recruiting clinician and/or researcher in consultation with the patient and their family. This variation in involvement in consent decisions (and in information provision) is no different to that involving standard age gradated trial printed participant information materials (and which will occur in the PIS-only arm of the embedded trials).

We will recruit host trials through several channels, including established links to UK clinical trials units that specialise in running trials involving children and adolescents. In addition, we will work with the relevant Clinical Research Networks (cancer and children),and through trial funders. We will also contact trial investigators as funding decisions are announced, for example from NIHR and MRC. Finally we will publicise the TRECA project through established trial networks and by presenting at conferences, such as the MRC Trials Methodology Hub. We will recruit host trials during Phase 1 of the study, given the long lead in of healthcare trials for research ethics and governance.

8.3 Delivery of interventions

Child and adolescent patients and/or a parent will be given the printed PIS only (as is usual) when allocated to that arm of the embedded trial.

Those allocated to the intervention arm will receive either the printed PIS and be given access to the MMI(s) or they will receive access to the MMI(s) alone. For those who receive both, we will not determine the order in which participants access the PIS and MMI and will leave this for the host trial to determine, to suit the practical demands of patient recruitment. However we will ask the host trial to record the order in which participants are given and access the PIS / MMI, and report this observation in the report of each embedded trial. The MMIs will be presented in the clinic on a computer or on a dedicated tablet computer. Participants will also be able to access the MMIs at home (via smartphone or a tablet or PC). In some circumstances, home viewing will take place before the patient's decision on clinical trial participation has been taken. Some patients will also want to be given access to the MMI after they have decided to take part in the host healthcare trial, just as they would if they had been given standard printed information only.

8.4 Outcome measures

Objective measures are the rates of recruitment to, and retention in, each host trial. For recruitment we will calculate the proportion of patients who agree to participate from the total approached, for each arm of the embedded trial. We will assume that patient eligibility for host trial participation will have been assessed before an approach has been made. For the retention outcome we will obtain data on the number and timing of drop outs from each host trial.

We will also measure the quality of decision making by potential host trial participants. Children and adolescents will be asked to complete a brief decisional scale, adapted from one used within the REFORM trial (unpublished data; P Knapp, P Bower, J Graffy, J Rick, S Cockayne) and drawing conceptually on the SURE [48, 49] and DelibeRATE scales [50]. When a parent or parents have been involved in the participation decision, we will also ask them to complete the scale. As far as is possible, we will adapt the scale to facilitate completion by young children.

As far as is possible, we will aim to obtain decision quality scores both from individuals who decide to participate in the host trial and those who decline.

8.5 Data collection

In patients who decide to take part, the children and adolescents and/or parent will be asked to complete the decisional scale once the host trial participation documentation has been completed. In

patients who decline participation, they will be asked to complete this measure in the clinic or will have them posted at home, as appropriate.

Data on recruitment to the host trial will be recorded automatically within the host trial dataset. Data on trial retention will also be recorded automatically within the host trial dataset, and is usually taken to mean the availability of data for the primary variable. Variation between host trials is likely, both in terms of the length of intervention period and follow-up; consequently the definition of 'retention' will vary. Having a single retention period common to all embedded trials would strengthen the meta-analysis, by removing one source of heterogeneity. This could be achieved by recording retention at the same time in all embedded trials, for example 6 months after recruitment, although this may prove impractical. However decisions on timing will be taken once we have recruited host trials to TRECA and have assessed their timetables. We would aim to exclude reasons for non-retention that were outside the control of the patient, in determining the availability of primary outcome data. The calculation of retention in the meta-analysis will be undertaken using relative effects, to reduce levels of heterogeneity.

In order to assess any potential moderating influences of other variables on the effectiveness of the MMIs, we will aim to obtain data within each host trial of children and adolescents age, gender and postcodes (as a proxy for socio-economic status), according to allocation in the embedded trial and to host trial participation decision.

8.6 Data analysis and sample size calculation

The primary objective of the TRECA study is to increase recruitment to clinical trials, thus the study sample size calculation for the host trials is the number of people approached to participate, rather than the numbers recruited.

The sample size calculation is based on the expected baseline recruitment rate of the host trials (that is, their recruitment rate without the intervention). As the host trials are yet to be determined, we have assumed a baseline recruitment rate of 20% to 80%, to account for the known variation in trial recruitment rates. Given this uncertainty, we have estimated the sample size based on the relative effect of the MMI alone (when compared to PIS alone). Further, we have assumed 80% power at standard 5% Type I error (α rate) to detect the specified effect and we have characterised the effect size as an odds ratio, which is more robust for sample size calculation.

Assuming the typical recruitment rate is 20%, an odds ratio of 1.2 would mean an increase in recruitment rate using the MMI to 23.1%. To detect this in a single randomised controlled trial (with 1:1 randomisation between MMI and printed material arms), a sample size of 701 would be needed. If the typical recruitment rate is 80%, an odds ratio of 1.2 corresponds to an increase in recruitment rate to 82.8% and would require a sample size of 783.

Results from each embedded trial will ultimately be combined in a meta-analysis. Given that there will be different trials with variation in interventions, participants and baseline recruitment rates, it is plausible that the effectiveness of the MMIs at improving recruitment will vary; i.e. there will be heterogeneity in the observed odds ratios across trials. Adjusting for this is approximate (particularly as the heterogeneity is currently unknown), however, as a rough rule of thumb if the I^2 statistic in the meta-analysis is 50% the sample size will double [51].

Given the three arm randomisation (with two of the arms being compared for the primary analysis), an additional 50% of people will need to be approached (i.e. 783 x 1.5 = 1,175). Furthermore, the adjustment for heterogeneity in effects of the MMI intervention across the six trials (estimated I-square value = 50%) means that the sample size should be doubled (i.e. 1,175 x 2 = 2,350).

Therefore the six embedded trials in TRECA should (on average) each be approaching 392 people, assuming a baseline trial recruitment rate between 20% and 80% of those approached. We will make

pragmatic decisions about inclusion, in part to attain variation among the included trials in aspects of the intervention and setting, and in part to ensure that we recruit a full complement of embedded trials to TRECA. Further, trials involving children and adolescents are often relatively small: our random sample survey of 100 trials involving children and adolescents with long-term conditions [3] found that only two-thirds had a target sample size of >216. Given the other entry criteria applied to host trials, one or more of the host trials recruited to TRECA may have a smaller target sample size than 216. Consequently the meta-analysis of the 6 embedded trials may be required to provide a robust evaluation of the MMIs' effectiveness.

9. Phase two sub-study

One of the host trials for TRECA is the Bone Anchored Maxillary Protraction (BAMP) trial. This trial is recruiting children and adolescents aged 11-14 years with the condition known as 'reverse bite'. Reverse bite is usually corrected with an operation at 17 years. The trial is investigating whether an operation that can be done at age 11-14 years can correct reverse bite. Participants in the BAMP trial are randomised to receive either an operation at age 11-14 years or not having the operation, to see whether having this operation at age 11-14 will mean not needing another more complicated operation at age 17.

The BAMP trial is recruiting small numbers of children and adolescents; currently four children and adolescents have been randomised to receive information about BAMP through TRECA (PIS; MMI; or both PIS and MMI) since February 2018. In addition to the small numbers being approached about BAMP using TRECA, there are approximately 30 children and adolescents per week attending the clinic at Tameside and Glossop Integrated Care NHS Foundation Trust who are ineligible for BAMP but who could provide an evaluation of the information provided about BAMP in the PIS and MMI formats.

The clinicians involved in recruiting to BAMP at Tameside and Glossop Integrated Care NHS Foundation Trust will approach children and adolescents aged 10-14 years of age who are attending the clinic at Tameside and Glossop Integrated Care NHS Foundation Trustfor review appointments. These children and adolescents would be approached by the clinicians and have a conversation about the purpose of the sub-study and be provided with a printed PIS about the purpose of the sub-study – that we are interested in understanding children and young people's preferences for information about a clinical trial - and an assent form (also signed by the parent or carer). Those approached will be told that this is a hypothetical scenario and if they agree, they will be randomised using physical sealed envelopes to receive information about the BAMP trial via printed PIS or via MMI. A tablet computer is located at Tameside and Glossop Integrated Care NHS Foundation Trust that would be used to allow those randomised to the MMI to view it whilst waiting for their appointment. After the participant has viewed information about the BAMP trial via either PIS or MMI, they will be asked to complete the decision-making questionnaire that has been approved previously by REC and HRA but has been re-worded slightly to reflect the hypothetical nature of the sub-study. The decision-making questionnaires seek respondents' evaluatons of the information and test whether the way the information is presented enables the person to make a more informed decision.

We will seek to recruit 148 participants to this sub-study (74 in PIS group and 74 in MMI group). This is to allow for 20% of those randomised not being able to complete the questionnaires (e.g. due to time available or not completing all questionnaires). The questionnaires have 9 Likert scale questions with each of these questions having a score option of 0-4, so the total possible score range is 0-36. A difference between groups (MMI versus PIS) of 4.5 (reflecting a mean of 0.5 point different on each of the 9 questions with a Likert scale) would be meaningful. Standard deviation (SD) on the scale of pooled scores is 6.75 (estimated that 95% scores would fall between 4.5 and 31.5 is 27. Dividing 27 by 4 for approx SD = 6.75). Power is 90% and significance level = 0.01.

Tameside and Glossop Integrated Care NHS Foundation Trust will collect and hold the assent forms for this sub-study. The University of York (TRECA team) is the data controller and will only be provided with anonymised data in the form of completed decision-making questionnaires from those who agree to participate in the TRECA sub-study. An agreement between Tameside and Glossop Integrated Care NHS Foundation Trust and the University of York is in place to describe this arrangement. Data provided to the University of York will include TRECA sub-study participant ID number, age, date questionnaire given and their answers to questions about the information they received about the BAMP trial.

10. Dissemination and projected outputs

The results of the research will be published in peer-reviewed academic journals, potentially targeting a number of audiences: trial and health services researchers; clinical audiences pertaining to each host trial; as well as information science, new media design and PPI audiences.

We will explore the potential for dissemination via the NIHR Clinical Research Networks, as well as the MRC Hubs for Trial Methodology.

The work will be disseminated at conferences with academic and clinical audiences. We will also aim to present findings at NHS centres that assisted with participant recruitment in Phase 1 and Clinical Trials Units that hosted an embedded trial.

Where possible we will also use social media to publicise the findings. In particular we will aim to engage with health charities, self-help groups and lobbyists, with a view to informing children and adolescents with a variety of conditions who might be involved in research.

The research should produce a large number of traditional academic outputs, including:

- Study protocol paper;
- Paper reporting the qualitative study in phase 1;
- Paper reporting the user testing and MMI revisions in phase 1;
- 6 papers reporting each of the embedded trials;
- A paper reporting an overview of findings and, if possible, a statistical meta-analysis of the embedded trials.
- A paper reporting the process and impact of PPI on the project.

The findings of the 6 nested trials will also have potential to be incorporated in the two Cochrane reviews on recruitment and retention strategies in trials, for which there is currently a lack of evidence relating to children and adolescents [9, 10].

11. Plan of investigation and timetable (Project start 1st February 2016)

Pre-start:

- Form PPI group; involve in REC material preparation
- Initial enquiries to CRNs, CTUs, funders re potential Phase 2 host trials
- Appoint researchers

February 2016 – January 2017 (Year 1)

- REC and HRA application for Phase 1 study 1 (March 2016)
- Confirm expert advisors (May 2016)

- Train PPI members for focus group & steering group work (June 2016)
- Commission provider for MMIs (June 2016)
- Submit protocol paper to journal (June 2016)
- Conduct 1st round of qualitative data collection (Phase 1) June 2016; data transcription & begin analysis (initial: June 2016)
- PPI & steering group meetings (June 2016)
- MMI development (June 2016– January 2017)
- Enquiries to CRNs, CTUs, funders re potential Phase 2 host trials (March 2016 – December 2016)
- Ethics application for Phase 1 User Testing study (July 2016)
- Conduct 2nd round of qualitative data collection (October 2016 -January 2017); data transcription & begin analysis (October 2016 onwards)
- PPI & steering group meetings (October 2016)

February 2017 – January 2018 (Year 2)

- Revise MMIs (January/February 2017) Conduct 1st round of User Testing (March 2017); analyse data; revise MMIs (March 2017)
- Conduct 2nd round of User Testing (June 2017); analyse data; revise MMIs
- Identify and confirm initial host trials for Phase 2 (March 2017 – January 2018)
- REC approval (overarching) for phase 2 of study (February 2017)
- Work with 6 host trials; generate trial-specific MMI content; finalise MMIs (June 2017 onwards)
- Submit REC substantive amendment for each embedded trial (December 2017 onwards)
- PPI & steering group meetings

February 2018 – January 2019 (Year 3)

- Begin participant recruitment to embedded trials; collect data on recruitment & decision quality (February 2018)
- Conference presentation & submit qualitative paper to journal (February/March 2018)
- Continue participant recruitment to embedded trials; complete collection of recruitment & decision quality data
- Collect trial retention data from host trials
- Conference presentation; submit User Testing paper to journal (June 2018)
- Submit second qualitative paper (January 2019)
- PPI and Steering group meetings
- Continue host trial retention data collection
- 2 conference presentations

- Presentations at centres involved in study

February 2019 – July 2019 (Year 4)

- Final PPI and Steering Group meetings
- Complete host trial data collection
- Conduct meta-analysis
- Write final report for NIHR
- Submit embedded trial papers & meta-analysis paper to journals
- Further conference presentations (funding permitting)

12. Project management

The project will be managed by Dr Jackie Martin-Kerry (1.0wte) with support from research fellow, Dr Rebecca Sheridan, who worked 0.5wte on the project. The immediate project team will be completed by Dr Peter Knapp, who will work 0.2wte on the project throughout. The project team will meet weekly throughout to review study progress. The project team will be joined for meetings by key members of the co-investigator team, as required, according to project stage. Administrative support will be provided by Sandi Newby, in the Department of Health Sciences at the University of York.

The project will be advised by a team including all co-investigators, two external expert advisors (Professor Bryony Beresford and Professor Michael Beresford), 1-2 PPI representatives, as well as a senior academic advisor from the University of York (Prof Ian Watt), who will chair the meetings. A TRECA steering committee will be established to steer the study and will at least four times over the study, with additional meetings by phone or video teleconference, as required.

Co-investigator Team

Dr Peter Knapp (PI)	Hull York Medical School and University of York
Dr Paul Baines	Alder Hey Hospital NHS Trust
Professor Peter Bower	University of Manchester
Professor Carrol Gamble	University of Liverpool
Dr Jonathan Graffy	University of Cambridge
Professor Steven Higgins	University of Durham
Ms Jennifer Preston	University of Liverpool
Dr Catherine Stones	University of Leeds
Professor Bridget Young	University of Liverpool

13. Research ethics and governance

The two studies in Phase 1 will each require standard REC approval.

Approval to conduct the 6 nested trials will be sought by substantial amendment application to the RECs that have already approved the individual host healthcare trial. This will happen after the trials have been recruited to the TRECA project, at the start of Phase 2 of the study.

Participants in the nested trial will not be informed that a trial of information provision is being undertaken. This approach has been used successfully in the MRC START project, in which recruitment to adult trials was evaluated, with RECs accepting the three arguments that:

1. to explain a nested information trial AND a host clinical trial to patients would be impractical and confusing;

2. to fully explain the nested information trial would potentially contaminate its evaluation of the interventions; and

3. both groups in the comparison receive the minimum required standard of information (with one group receiving enhanced information), and thus there is no strong ethical imperative for full disclosure.

We will apply for full research ethics approval for patients not to have the opportunity to give informed consent to enter into the embedded recruitment study on the basis that the embedded trial is not withholding information, simply changing the way it is presented.

Each embedded trial will be registered by the host trial as a sub-study on ISRCTN.

14. Financial and insurance issues

TRECA is funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research Programme (NIHR HS&DR 14/21/21). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

TRECA is sponsored by the University of York. Each host trial will have its own University sponsor. Normal NHS indemnity procedures will apply.

15. Patient and Public Involvement

Active Patient and Public Involvement (PPI) in the study will take four forms.

1. We will continue to use the expertise of the NIHR Alder Hey Clinical Research Facility (CRF) Young Person's Advisory Group throughout and via the national GenerationR Young Person's Advisory Group as required (see www.generationr.org.uk).

2. We will form a small PPI advisory group, comprising 3 children or adolescents with long-term conditions and 3 parents, who will meet before steering group meetings, to discuss project progress and planning. This group will be facilitated by one of the salaried researchers and JP.

3. We will also seek to involve one or two adolescents in the conduct of the focus groups during study Phase 1. Having the groups facilitated by 2 people, one of whom is a young person as PPI representative, should enhance data validity.

4. Finally we will seek to recruit several adolescents with long term conditions and parents in the dissemination of study results, particularly for presentations to centres conducting research involving children and adolescents.

PPI representatives will be trained and mentored in these activities by applicants PK and JP, and an NIHR Research Design Service PPI specialist.

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