CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

FULL STUDY TITLE: OP Non-STOP Study (Operative or Non-Surgical Treatment of Perthes' disease). A multi-centre prospective randomised superiority trial of containment surgery compared to optimised non-surgical care for Perthes' disease of the hip in children

SHORT STUDY TITLE: Operative or Non-Surgical Treatment of Perthes' disease

STUDY ACRONYM: OP Non-STOP

Version: 2.0_27Aug2024

Study Website: TBC

Contents

1 RESEARCH REFERENCE NUMBERS

Table 1: Research Reference number

Sponsor Protocol Number:	PID: AH23-10-003
Clinical Trials Unit (CTU) Reference:	OCTRU0403
Funder Reference(s):	NIHR152309
Ethics Reference Number:	24/WM/0157
IRAS Number:	318800
Registry:	International Standard Randomised Controlled Trial Number (ISRCTN): ISRCTN83315571
CPMS ID:	53594

2 ORGANISATIONAL INFORMATION

Table 2: Organisational Information

Chief Investigator (CI):	Professor Daniel Perry Professor and Honorary Paediatric Consultant Orthopaedic Surgeon Refer to the KEY STUDY CONTACTS section for contact details.
Sponsor:	Alder Hey Children's Hospital NHS Trust Refer to the KEY STUDY CONTACTS section for contact details.
Clinical Trials Unit:	The study is managed by the Oxford Trauma and Emergency Care Group. Oxford Clinical Trials Research Unit (OCTRU) Botnar Research Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LF Email: octrutrialshub@ndorms.ox.ac.uk
Funder:	The study is funded by the National Institute for Health and Care Research (NIHR) HTA programme (NIHR152309). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Refer to 32.2 Funding and support in kind section for full details of all funding sources.
Co-applicants:	The following are co-applicants on the study grant and have contributed to the study design and development of the protocol: **Mr Nicolas Nicolaou (Joint Lead Grant Applicant with Professor Perry)** Paediatric Consultant Orthopaedic Surgeon Sheffield Children's NHS Foundation Trust ✉ nicolas.nicolaou3@nhs.net **Dr David Keene** Associate Professor in Trauma and Orthopaedics & Physiotherapist University of Exeter ✉ david.keene@exeter.ac.uk **Mr Adam Galloway** Specialist Children's Physiotherapist and NIHR Clinical Doctoral Fellow University of Leeds ✉ adamgalloway@nhs.net **Dr Duncan Appelbe** Senior Research Information Specialist University of Oxford

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Additional protocol contributors:	**Dr Vicki Barber** OCTRU CTU Manager ✉ vicki.barber@ndorms.ox.ac.uk Produced first draft of protocol **Dr Marloes Franssen** Senior Trial Manager ✉ Marloes.franssen@ndorms.ox.ac.uk
Conflict of Interest statement:	None of the co-applicants/protocol contributors listed above have declared a potential conflict of interest
Confidentiality Statement:	In accordance with the NIHR Open Access policy, the protocol will be made freely and openly accessible to all.

3 KEY STUDY CONTACTS

Table 3: Key Study Contacts

Central study team/Coordinating centre for general queries	OP Non-STOP study team Oxford Trauma and Emergency Care Kadoorie Centre University of Oxford John Radcliffe Hospital Headley Way Oxford OX3 9DU ☎ 01865 227902 ✉ opnon-stop@ndorms.ox.ac.uk
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Trial Steering Committee (TSC) Chair:	Prof Catriona McDaid Professor of Applied Health Research ✉ catriona.mcdaid@york.ac.uk Other members of the TSC are detailed within a study specific TSC charter.

Data and Safety Monitoring Committee (DSMC) Chair:	Mr Robin Paton Honorary Secretary of the Royal College of Surgeons of Edinburgh and Retired Children's Orthopaedic Surgeon ✉ patonsquared@gmail.com Other members of the DSMC are detailed within a study specific DSMC charter.

4 PROTOCOL APPROVAL/SIGNATORIES

This protocol has been approved by the Sponsor, Chief Investigator (CI) and Lead Study Statistician. Approval of the protocol is documented in accordance with the Oxford Clinical Trials Research Unit (OCTRU) Standard Operating Procedures (SOPs).
All parties confirm that findings of the study will be made publicly available through publication without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any important deviations and serious breaches of Good Clinical Practice (GCP) from the study as planned in this protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

Perthes' disease is a rare condition of the hip joint and one of the most disabling conditions affecting children. It has a profound impact on the life of the child, and that of their family.

The hip is a 'ball and socket' joint. This can be thought of as a scoop of ice-cream, with the ice-cream (the 'ball') sitting in an ice-cream scoop (the 'socket'). Perthes' disease is caused by a problem with the blood supply to the hip, which means the ball doesn't get enough oxygen and nutrients to grow. When this happens, the hip loses its strength and flattens - like the ice-cream melting and becoming squashed. In Perthes' disease there is a temporary loss of blood supply, which means that after some months the nutrients return, and the ball again hardens. However, the bone remains whatever shape it was when it became squashed. This can lead to a ball that doesn't fit well into the socket, which can cause pain, limitation to usual activities and severe hip arthritis in childhood.

About half of the surgeons in the UK currently believe that surgery can be helpful in 'controlling' the way that the ball of the hip flattens, which could result in a better shaped hip and better outcomes for children. Surgery involves breaking the bone to re-orientate the ball to ensure that it deforms in a controlled way into the socket (called 'containment' surgery). The other half of surgeons do not undertake surgery, instead focusing on a package of care (called 'non-surgical or active containment') that involves physiotherapy, activity restriction and pain relief. Physiotherapy aims to maintain movement of the hip and keep the soft ball moving within the socket, allowing it to continually smooth its shape – i.e. the 'ice cream rolling within the scoop'. These surgeons believe that surgical containment is no better than active containment with the benefit that active containment does not expose the child to the unnecessary risks associated with surgery.

Given how disabling Perthes' disease is, and the differences in how it is treated, patients, families, and health professionals ranked the management of Perthes' disease in the top-five most important research priorities in children's orthopaedic surgery.

This study will compare children having 'containment surgery' to children having 'active containment' and specifically look at how well children are able to take part in activities three-years after joining the study.

216 children aged five years to twelve years inclusive with newly diagnosed Perthes' disease will be invited to take part in the study. Those who join will be split fairly into two groups, using a process called 'randomisation'.

At the end of the study, we aim to know if containment surgery is better than active containment for helping patients with Perthes' disease to be able to take part in activities.

6 STUDY SYNOPSIS

Table 4: Study Synopsis

Full Study Title:	OP Non-STOP Study (Operative or Non-Surgical Treatment of Perthes' disease). A multi-centre prospective randomised superiority trial of containment surgery compared to optimised non-surgical care for Perthes' disease of the hip in children
Short Title:	Operative or Non-Surgical Treatment of Perthes' disease
Study Acronym:	OP Non-STOP
Study Design:	The OP Non-STOP study is a multi-centre, two arm, parallel design, superiority, randomised controlled clinical study.
Study Aim	To evaluate the clinical and cost-effectiveness of containment surgery compared to best conservative care amongst children aged 5 to 12 years old with Perthes' disease of the hip.
Study Participants/ Target Population:	The OP Non-STOP study will recruit 216 children aged 5 to 12 years inclusive with newly diagnosed Perthes' disease. Refer to section 11 of the main body of the protocol for full eligibility criteria
No. of study arms:	Two
Intervention:	Containment surgery In this pragmatic study the surgeon should use the containment procedure that is familiar to them as per their usual practice (typically a femoral varus osteotomy, Salter osteotomy or shelf osteotomy).
Comparator:	Optimised Non-Surgical (active) Containment – The Non-STOP Package (Non-Surgical Treatment of Perthes' disease) Children and families will receive an individual face-to-face best practice therapy session of up to 90 minutes with a study-trained physiotherapist at the recruiting hospital/regional specialist centre.
Planned Sample Size:	216 participants
Target no. of research sites:	15 recruiting sites in the internal pilot increasing to a minimum of 28 recruiting sites for the main study.
Countries of recruitment:	United Kingdom (UK)
Study duration:	66 months
Planned recruitment duration:	Recruitment is expected to last for 30 months.

<table>
<tr><td>Duration of intervention:</td><td colspan="2">Each intervention in the study is a one-time intervention – surgery or the best practice conservative therapy session.</td></tr>
<tr><td>Follow-up duration:</td><td colspan="2">Each participant will be followed up for 36 months from randomisation.

Consent will be sought at recruitment to share details with the Non-Arthroplasty Hip Registry (NAHR) to enable long term follow up.</td></tr>
<tr><td></td><td>Objective</td><td>Outcome Measure</td></tr>
<tr><td>Primary objective and outcome measure:</td><td>To determine whether children treated with containment surgery have better lower extremity function than children treated with active containment</td><td>PROMIS - Mobility</td></tr>
<tr><td>Additional objectives and outcome measures:</td><td colspan="2">Refer to the OBJECTIVES AND OUTCOME MEASURES section of the protocol main body for full study objectives and outcome measures.</td></tr>
</table>

7 ABBREVIATIONS

Table 5: Abbreviations

AE	Adverse Event
BOSS	British Orthopaedic Surgery Surveillance
CAT	Computer Adaptive Test
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
COS	Core Outcome Set
COSMIN	Consensus-based standards for the selection of health measurement instruments
CRF	Case Report Form
CTU	Clinical Trials Unit
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MCID	Minimum clinically important difference
NAHR	Non-Arthroplasty Hip Registry
NHS	National Health Service
NIH	US National Institute for Health
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
PACS	Picture Archiving and Communication System
PI	Principal Investigator
PIS	Patient information sheet
PPI	Patient and Public Involvement
PROMIS	Patient-Reported Outcomes Measurement Information System
QALY	Quality-adjusted life-years
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
STOP	Surgical Treatment Of Perthes'
TIDIER	Template for Intervention Description & Replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
YPAG	Young Persons Advisory Group

Note: Throughout this protocol 'parents' is used as an inclusive term for parent/guardian/carer; 'family' is used as in inclusive term for parent/guardian/carer AND the child and "child" is used as an inclusive term for child/legal ward.

8 BACKGROUND INFORMATION AND RATIONALE

8.1 Background

Perthes' disease is an idiopathic avascular necrosis in a developing femoral head (ball of the hip joint). It occurs predominantly in males (male:female ratio 4:1) between 4 and 12 years old [1, 2]. The disease results in collapse of the bone within the femoral head, which results in severe pain and disability amongst affected children. Severe pain and disability continues until the hip re-ossifies; which is typically after 2-3 years [3]. Perthes' disease typically results in long-term deformity of the hip, which can cause longer term pain and disability and is a major precipitant of premature osteoarthritis; frequently necessitating a hip replacement in early adulthood [4]. Perthes' disease is one of the most common and most poorly understood disorders encountered by children's orthopaedic surgeons.

The UK has the highest incidence of Perthes' disease in the world, with children in Northern England, and particularly Liverpool, having the greatest risk of disease [2, 5, 6]. The lifetime cumulative risk of disease in the UK is around 1:1200 children, with around 500 new cases in the UK each year [6]. The origins of the disease are very closely linked to socioeconomic deprivation [2, 6, 7], though the aetiology and mechanism are unknown.

A key principle of Perthes' disease treatment is a process called 'containment'. As the head of the femur collapses, the belief is that it should be 'contained' within the acetabulum in order to allow it to re-ossify (re-develop) in the round shape of the acetabulum. Some surgeons perform surgery to facilitate 'containment' by redirecting the femoral head into the acetabulum (i.e. a femoral osteotomy, typically with a plate & screws and a 'spica' plaster cast) and others will direct/alter the shape of the acetabulum to better cover the femoral head (i.e. pelvic osteotomy, typically with internal wires and a 'spica' plaster cast); soft tissue releases (i.e. tendon releases) may also be performed to improve the range of movement. However, other surgeons believe that a package of care including physiotherapy, activity restriction and pain relief is equally as good at achieving 'containment'; called 'active containment'. This causes international controversy and uncertainty for children and their parents/carers.

8.2 Current practice – The British Orthopaedic Surgery Surveillance (BOSS) Study

Given the controversy, there is substantial variation in the treatment of Perthes' disease. This varies from observation without any intervention, to physiotherapy involving activity restrictions and physiotherapy, to surgery involving femoral and/or pelvic osteotomies [3, 8, 9]. Over the last 6 years, researchers in the UK, including the CI of this study, have carefully explored current practice through a nationwide collaboration with the support of parent co-investigators.

In 2016, the National Institute for Health and Care Research (NIHR) funded British Orthopaedic Surgery Surveillance (BOSS) Study, was the first UK study to investigate Perthes' disease [3]. This was a cohort study of incident cases of Perthes' disease. The study collected surgeon reported outcomes on all new cases of Perthes' disease from most children's orthopaedic surgeons in the UK over an 18-month period.

371 children (396 hips) with Perthes' disease were recruited during this time. Two thirds of cases were considered eligible for surgery, and half of these received operative 'containment surgery'. The decision for surgery was almost exclusively driven by the belief and recommendation of the surgeon; with some centres offering and undertaking surgery on the majority of children, whilst other centres did not offer surgery to any. Physiotherapy and advice regarding activity restrictions was the primary treatment in the majority (97%) of those treated without surgery.

The BOSS cohort identified 'clinical irritability' of the hip and 'age' to be the only consistent factors that influenced treatment choices amongst surgeons. Surgery was rarely performed on those under five years old and occurred in more than half of those aged over eight years old. Surgeons operated more frequently on hips that they assessed to be 'irritable' or 'stiff'. The study confirmed the findings of prior literature by demonstrating a worse radiographic prognosis associated with increasing age, female sex, and greater radiographic collapse. However, the 'stiffness' of the hip did not appear to influence outcome. Furthermore, the study found no evidence to suggest that containment surgery improved outcomes. The results of the BOSS study prompted the commissioning brief by the NIHR Health and Technology Assessment (HTA) that has funded this study (NIHR commissioned funding call – 21/586 Management of Perthes' disease in children).

8.3 Research to date

The BOSS study is currently the most robust investigation into the treatment of Perthes' disease. There are no randomised controlled trials comparing treatments, and treatment decisions are largely dependent on the beliefs of the treating surgeon. Prior to the BOSS study, only two other cohort studies had sought to prospectively identify the outcomes of children with Perthes' disease [8, 9]. Each concluded that surgery had a small positive influence on Perthes' disease in specific subgroups of patients. However, each of these studies were subject to significant selection bias, and their findings were made from post-hoc analyses exposing them to type I error through multiple hypothesis testing and the reporting of subgroups with novel positive findings. The consistent findings were that children younger than 5 years old, males and those with less severe radiographic collapse, have marginally better radiological outcomes, regardless of treatment; though it was unclear how this translates into patient reported outcomes.

Alongside the BOSS cohort, OP Non-STOP study investigators have worked to understand the impact of Perthes' disease on the lives of children and their families. A mixed-methods study was undertaken that included 18 parents and 12 children to understand how the disease impacted day-to-day life. Profound effects of the disease on play, school attendance, sleep and physical and social wellbeing were identified [10]. This work led on to these themes being developed with clinicians, and the involvement of a larger group of children and parents throughout the world to create a Core Outcome Set (COS) for Perthes' disease [11]. In addition to the domains within the COS, surgeons emphasised the importance of radiological outcomes, particularly the femoral head shape, in trying to assess the likely longevity of the hip joint before the need for arthroplasty, as femoral head shape may be used to predict failure of a native hip joint.

8.4 Evidence why this research is needed now

The James Lind Priority Setting Partnership, and a separate priority setting exercise of the British Society of Children's Orthopaedic Surgery, has identified the need for surgery in Perthes' disease as one of the top research priorities in children's orthopaedic surgery [12, 13].

Furthermore, the BOSS study generated huge enthusiasm amongst clinicians and patient groups. This has created an excellent environment in which to definitively address the effectiveness of surgery in this childhood disease.

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The aim of this randomised controlled superiority trial is to evaluate the clinical and cost-effectiveness of containment surgery compared to active containment amongst children aged between five and twelve years (inclusive) with Perthes' disease of the hip.

9.2 Primary objective and outcome measure

Table 6: Primary objective and outcome measure

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To determine whether children treated with containment surgery have better lower extremity function than children treated with active containment	PROMIS Mobility Computer Adapted Tool (CAT)	Baseline and primary endpoint at 36 months post randomisation	PROMIS mobility score	Case report Form (entered directly into the REDCap study database)

9.3 Choice of primary outcome/justification for the follow-up period

Families were integral to inform the development of this study. Their input was taken along with evidence from the BOSS cohort, the qualitative work encompassing interviews with families and the developed core outcome set. All of this identified that physical function is most impacted amongst children with Perthes' disease and is therefore the most appropriate primary outcome in research.

The most appropriate outcome measure to test this domain has been identified to be the Patient-Reported Outcomes Measurement Information System (PROMIS) Mobility tool. In general, 'PROMIS scores' are a collection of patient-reported health status tools available for children and adults that were developed to be disease non-specific in collaboration with the US National Institute for Health (NIH). These tools can be administered to healthy children as well as to those with a variety of chronic health conditions. The PROMIS Paediatric item banks were developed using a strategic item generation methodology adopted by the PROMIS Network utilising item response theory. Field-testing occurred among 4129 children aged 8 – 17 years. Lower T-scores indicate a worse functional outcome. PROMIS is available in full (30 questions), short-form (8 questions) or as a CAT (average 8-questions). A CAT enables the answer from one question to inform the choice of the next and so each child could answer a distinct set of questions to arrive at their score.

A consensus-based standards for the selection of health measurement instruments (COSMIN) exercise advocated the use of the PROMIS tools in children's orthopaedic research, and experimental data demonstrates that PROMIS mobility strongly correlates with measured activity [14]. PROMIS-CATs have been used successfully in other NIHR-HTA trials led by members of the OP Non-STOP team, including SCIENCE, FORCE and CRAFFT [15].

The original version of the tool was a proxy (parent) reported version developed for children 8– 17 years old [16], which was subsequently validated in the younger population [17]. A self-reported version of the tool is available for use in older children. However, the PROMIS development team do not recommend combining the use of self-reported outcomes and proxy-reported outcomes. The proxy version of PROMIS Mobility is therefore the only outcome that covers the age spectrum within the study population. We will therefore seek a proxy report of PROMIS for all participants in this study. This approach will allow all outcomes to be combined in the analysis, irrespective of age.

The primary outcome measure for this study is Patient Reported Outcomes Measurement

Information System Mobility Score for Children (PROMIS-Mobility) at 3-years post randomisation. PROMIS-Mobility CAT is a validated tool to assess lower extremity function in children [18, 19].

The timepoint of 3-years reflects a typical time at which the inflammation and irritability associated with the disease process are subsiding, with ongoing restriction thereafter unlikely to notably improve spontaneously.

9.4 Secondary objectives and outcome measures

Table 7: Secondary objectives and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To compare lower extremity function in both groups	PROMIS Mobility CAT	Baseline and 3, 6, 9, 12, 18, 24, 30 and 36 months post randomisation	PROMIS mobility score	Case report Form (entered directly into the REDCap study database)
To compare pain levels in both groups	Wong Baker Faces Pain Scale	Baseline and 3, 6, 9, 12, 18, 24, 30 and 36 months post randomisation	Wong Baker Faces Pain Scale score	Case report Form (entered directly into the REDCap study database)
To compare Quality of Life, Activities of Daily Living, Sleep and Psychological Impact in both groups	CHU-9D Questionnaire	Baseline and 3, 6, 9m 12, 18, 24, 30 and 36 months post randomisation	CHU-9D score	Case report Form (entered directly into the REDCap study database)
To compare impact on family life in both groups	PROMIS family relationships tool	Baseline and 3, 6, 9, 12, 18, 24, 30 and 36 months post randomisation	PROMIS family relationships score	Case report Form (entered directly into the REDCap study database)
To compare educational participation in both groups	Non validated questionnaire on school absence	3, 6, 9, 12, 18, 24, 30 and 36 months post randomisation	Days of school absence	Case report Form (entered directly into the REDCap study database)

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To compare the complication rate, particularly considering the need for future operative interventions in both groups	Non validated questionnaire on complications	6, 12, 18, and 36 months post randomisation	Frequency of pressure sores, non-union of the bone, wound or bone infection, major injury to nerves altering lower limb function, implant-related fracture, metalwork fracture/failure, need to remove/adjust metal implants, total hip arthroplasty (replacement)	Case report Form (entered directly into the REDCap study database) Medical notes
To estimate cost-effectiveness, from the UK NHS and Personal Social Services perspective in both groups	Non validated resource use questionnaire and CHU-9D	Baseline (CHU-9D only), 6, 9, 12, 18, 24, 30 and 36 months post randomisation	Resource use from hospital and out of pocket expenditure from families. CHU-9D score	Case report Form (entered directly into the REDCap study database)
To quantify the degree of residual deformity (waldenstrom grade and Stulberg classification)	Measured from routinely collected images of the hip or pelvis harvested from the picture archiving system.	An image of the hip or pelvis harvested from the picture archiving system within a 6 month timeframe of the primary outcome (36 months).	Routinely collected images of the hip or pelvis harvested from the picture archiving system.	Medical notes

9.5 Choice of secondary outcomes

***PROMIS Mobility*.** As per section 9.3 Choice of primary outcome/justification for the follow-up period

Wong-Baker FACES Pain Scale [20] - The Wong-Baker faces pain score is a validated self-reported tool that will be self-reported amongst all children in the study. It is an ordinal assessment of pain outcomes, using a series of six facial-expressions to illustrate the degree of pain intensity. A numerical rating is assigned to each face (from 0 - 'no hurt' to 10 – 'hurts worst'). It has been validated for use amongst children over 3-years-old, including in the Emergency Department setting [21]. It is particularly useful in children, as only one third of children up to 14 years understand the concept of a visual analogue scale [22]. The Wong Baker Faces Pain Score has been demonstrated to be useful in older children aged 8-17 years old, correlating closely with other pain tools, such as VAS [21]. The OP Non-STOP study team have also used this scale previously and found almost identical scores amongst children <8 years and those aged 8-16 [23]. This tool has the advantage that it can be self-reported amongst all participants in the study as it is validated for self-reported use from 5 years old [16, 17].

Child Health Utility-9D (CHU-9D) [24]. - The CHU-9D is a paediatric preference-based measure of health-related quality of life, consisting of 9 domains each with a 5-level response. This will be used to elicit health utility for the cost-utility analysis. For consistency with the primary outcome measure we intend to conduct all measurements via proxy. Valuation will estimate Quality-adjusted life-years (QALYs) using an area under the curve approach with preference weights derived for the UK population. In addition to the cost utility analysis, we will report the components of CHU-9D separately as these measure several elements of health that families have indicated that they are particularly interested in, through the core outcome set (i.e. sleep disturbance, psychological impact and activities of daily living).

PROMIS Pediatric Family Relationships [25] - This has been highlighted as an important outcome within the core outcome set. The complex role of families in child and adolescent health and their role in the management of chronic conditions however has been hampered by a lack of validated measures of family relationship experiences. This instrument addresses this gap, with item banks and short forms developed using a rigorous mixed-method approach consistent with PROMIS standards.

Educational participation - Parents will be asked to indicate the number of days their child did not participate in educational activities due to their Perthes' disease.

Complications - All complications related to the disease and its treatment will be recorded.
The complications anticipated in the management of these patients (particularly considering readmission or subsequent surgery) include pressure sores, non-union of the bone, wound or bone infection, major injury to nerves altering lower limb function, implant-related fracture, metalwork fracture/failure, need to remove/adjust metal implants, total hip arthroplasty (replacement).

Resource use - Participants' use of primary, secondary and community care services, as well as medications will be collected using a bespoke electronic resource use questionnaire. In addition, parental absence from work and additional days of purchased childcare will be collected.

Radiographs **-** This study will harvest routinely collected images of the hip/ pelvis available on the Picture Archiving and Communication System (PACS) taken pre-operatively, post-intervention and the most recent at 3 years post randomisation. These routine images will be stored in a bespoke application (TRIAGE) hosted at the University of Oxford and used to quantify the degree of residual deformity by an independent assessor, using the Stulberg classification for all hips in the Waldenstrom 3B (late re-ossification) or 4 (healed) stage of disease.

9.6 Exploratory objectives (to be reported and funded separately)

There are no additional exploratory/mechanistic objectives/outcomes in this study. However, all OP Non-STOP participants will be asked to give their consent for their personal details to be shared with the Non-Arthroplasty Hip Registry (NAHR); which is the national UK registry of hip surgery that does not involve joint replacements. Registration on the NAHR will enable long term follow up of study participants at a later time point. This follow-up falls outside the scope of this trial and additional approvals and funding would be required for any future research.

10 STUDY DESIGN AND SETTING

The OP Non-STOP study is a multi-centre, two arm, parallel design, superiority, randomised controlled clinical trial.

The study will recruit 216 children (108 in each of two arms) with Perthes' disease from a minimum of 28 sites in the UK. Participants will be randomised to receive either containment surgery or active containment.

A study flow chart is provided in APPENDIX 1 – STUDY FLOW CHART.

10.1 Recruiting sites/site types

Participants will be recruited from a minimum of 28 orthopaedic departments who have surgeons specialising in the treatment of childhood disease.

Treatment of all severities of Perthes' disease tends to be focused in specialist units in the UK. Sites that have been identified as potential recruiting sites for this study have seen between 3 and 20 eligible cases per year.

Refer to section 27 for information on identification and management of sites.

10.2 Collection of outcome data and follow-up assessments

Data will be primarily collected electronically. The study will be made efficient by ensuring that all outcomes are collected via a SMS text message with a link to an electronic Case Report Form (eCRF) amongst those with a smart phone or an e-mail link to an eCRF for those with internet access but no smart phone. If needed, questionnaires can be completed in clinic with the research team at site or over the phone with the central team.

Study materials will be optimised using age-appropriate multimedia resources, developed with knowledge acquired through members of the OP Non-STOP teams work as part of the NIHR TRECA study [26].

10.3 Countries of recruitment

UK.

10.4 Duration of participant involvement

Participants will be in the study for approximately 36 months from randomisation to last protocol visit.

10.5 Post-study treatment/care and follow-up

Following a participant's allocated containment surgery or active containment, they will receive standard NHS care. All patients will receive analgesia as per local/best practice guidelines and physiotherapy where required.

10.6 Central review procedures

The degree of residual deformity will be quantified (Waldenström grade and Stulberg classification) on the central review CRF.

10.7 Use of Registry/NHS England data

Parents and children will have the option to consent to their contact details and the child's personal details being shared with the NAHR; which is the national UK registry of hip surgery that does not involve joint replacements. Registration on the NAHR will enable long term follow-up of study participants at a later time point. This follow-up falls outside the scope of this study and additional approvals and funding would be required for any future research.

10.8 Expected recruitment rate

The pilot phase will involve recruitment in 15 centres over a 12 month period. The main recruitment phase will then continue for an additional 18 months and at least 28 centres.

Recruitment projections, informed by data from the BOSS study, are based on a recruitment rate of 0.35 participants per site per month.

10.9 Equality, diversity and inclusion for study participants

There is a very strong socioeconomic gradient in Perthes' disease, with deprived White communities predominantly affected. We are aware, through the prior BOSS study, of the centres that have a particularly high burden of disease; we will therefore prioritise centres serving deprived communities (particularly in the North West and North East of England) and optimise the research processes to best engage this participant group [27].

The team have carefully considered digital inclusivity, particularly given the socioeconomic gradient associated with Perthes' disease. Both children and families in the study advisory groups had a strong preference for electronic media and data collection, rather than paper, and did not feel that the use of email/ smartphones would be a barrier to recruitment or follow-up. This is backed up by a recent publication on digital inclusion for UK children [28]. However, paper copies of study documents will be made available when requested. The PROMIS Mobility primary outcome tool must be collected electronically (as this is a computer adaptive test), so to facilitate this, families can choose to be followed up by telephone if more convenient.

During the early phase of the COVID-19 pandemic, 8% of children (aged 3 – 17 years) did not have home access to a desktop computer, laptop or netbook which is connected to the internet. However, when access to smartphones in a household was accounted for, this rate was lower than 1% of households [29]. Our other HTA trials (FORCE, SCIENCE, CRAFFT) have recruited patients in similar paediatric orthopaedic populations using email and smartphone technology throughout; with all digital materials optimised for use on smartphones. During the internal pilot, we will monitor for any issues by analysing screening logs and exclusion reasons.

10.10 End of study

The end of study is the point at which all CRF and non-CRF data relating to the study primary and secondary outcomes has been entered/received (or collected if non-CRF data) and all queries resolved. The study will stop randomising participants when the stated number of patients to be recruited is reached.

The Sponsor and the CI reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

11 PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI).

11.1 Timing of eligibility assessment

Eligibility will be assessed upon initial entry into the study and confirmed at the point of randomisation.

11.2 Overall description of study participants

The OP Non-STOP study will recruit children aged 5-12 years old with Perthes' disease.

Written informed consent/assent must be obtained before any study specific procedures are performed.

11.3 Inclusion Criteria

A patient will be eligible for inclusion in this study if **ALL** of the following criteria apply:

- Radiographic evidence of Perthes' disease,
- Radiographs demonstrate that the disease is in the initial, sclerotic or fragmentation stage,
- Aged 5 to 12 years inclusive,
- Willing and able to give informed assent/consent.

Note: Patients may be enrolled with bilateral Perthes' Disease - though patients can only ever be enrolled once into the study. If one side has old disease (i.e. hip in reossification or healed stage of disease) and is not already included in the study, then the newly affected hip can be enrolled (i.e. that hip in the initial, sclerotic or fragmentation stage*). If both hips have new disease, then the hip considered the most severely affected will be considered the hip of interest and the surgeon must specify which hip is the unit of randomisation.*

11.4 Exclusion Criteria

A patient will not be eligible for the study if **ANY** of the following apply:

- There is evidence that the patient and/or parent would be unable to adhere to the study procedures or complete follow-up, such as insufficient comprehension,
- Child has undergone prior containment surgery on the affected hip (i.e. the hip to be randomised),
- The child has previously been enrolled into the OP Non-STOP Study.

11.5 Rationale for inclusion and exclusion criteria

The stage of disease ensures that the hip remains 'plastic' (i.e. is in a stage of disease whereby it would be amenable to treatment with containment).
The age of disease reflects the group for which there is clinical equipoise.

11.6 Pre-study screening tests or investigations

There are no pre-study screening tests for inclusion in the study.

11.7 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a randomised study. There will be no waivers regarding eligibility (i.e. each participant must satisfy all the eligibility criteria). Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient onto the study, the PI or designee will confirm eligibility. If unsure whether the potential participant satisfies all the entry criteria and to clarify matters of clinical discretion investigators should contact the OP Non-STOP central study team, who will contact the CI or designated clinicians as necessary. If in any doubt, the CI or joint lead grant applicant must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF)/Trial Master File (TMF).

11.8 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact can be made with the OP Non-STOP central study team for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries may also be directed to the central study team. Minor administrative corrections or clarifications will be communicated to all study investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 28.8 Urgent safety measures.

12 SCREENING AND RECRUITMENT

Participation will be offered regardless of the patients' or their parents' gender, sexual orientation, ethnicity, religion or belief, disability, or socio-economic status.

12.1 Participant Identification

Participants will be screened and then approached for potential recruitment from a minimum of 28 NHS hospitals in the United Kingdom.

The following methods will be used to identify potentially eligible participants:

- Identification during routine orthopaedic out-patient clinic visits and/or acute admissions

All patients with new radiographic evidence of Perthes' disease will be assessed for eligibility by a member of the research team.

12.1.1 Identification of participants during routine orthopaedic out-patient clinic visits and/or acute admissions

Potentially eligible patients and their parents identified during routine orthopaedic out-patient clinic visits and/or acute admissions at participating centres will be provided with the participant information material (i.e. a link to the study website and access to the patient information materials) by a member of their usual care team (who may also be a member of the site research team) and asked to consider the study.

Where their usual care clinician is not a member of the site research team, potential participants will be asked if it would be acceptable for their name and contact details to be passed to the site research team. If acceptable, the research team will make contact at a later time point (this may be in person in a clinic or via telephone or video call in accordance with local site practice) or during a further routine clinic visit. Potential participants may also be given the online PIS.

Potential participants and their parent are approached for permission for their details to be passed onto the site research team – if this permission is given this should be recorded in their clinical notes.

12.1.2 Identification through study advertising material

Social media might be used to advertise the study. All patient facing materials will be approved by REC/Health Research Authority (HRA) prior to use.

12.2 Re-screening if a potential participant does not meet inclusion/exclusion criteria first time round

If a potential participant does not meet the inclusion/exclusion criteria at first assessment, they can be re-screened – there is no time limit on when this can occur.

12.3 Use of screening logs

A screening log (within the REDCap study database) will be used to record information about the number of patients assessed for eligibility and reasons for exclusion or declined consent. Personal identifiable data will not be recorded on the screening log; a screening number will be assigned to each patient screened. The screening logs will contain non-identifiable information such as the child's age, sex, deprivation score and ethnicity.

Screening data will be reviewed each month by the study management team to assess whether representative samples of patients are being approached and to ensure no selection bias occurs in any of the centres with regard to the inclusion/exclusion of specific groups of patients.

Continued training of site staff on accurate and inclusive screening and recruitment will be through newsletters, regular Q&As/top tips, and refresher sessions. Investigator meetings will be planned, as they have proved successful in the past in ensuring appropriate sampling of patients.

13 STUDY INTERVENTION AND COMPARATOR

Participants will be randomised to either:

13.1 Containment surgery (intervention)

Participants randomised to containment surgery will receive an operation on their hip, which will typically be undertaken within three months of randomisation.

All participating centres are familiar with the surgical technique. The surgical technique seeks to embrace the vulnerability of the plastic epiphysis by ensuring it rests firmly within the acetabulum during femoral head collapse. This is achieved through an osteotomy, which includes either an osteotomy to the femur and/or pelvis (typically a femoral varus osteotomy, Salter osteotomy or shelf osteotomy). Soft tissue releases may also be performed alongside the osteotomy surgery. *These surgical interventions are amongst the most common interventions performed in children's orthopaedic surgery and are therefore familiar to all children's orthopaedic surgeons.* In this pragmatic study the surgeon should follow the technique that is familiar to them as per their usual practice.

Post-operative care will follow local practice. After surgery a period of restricted weight bearing on the affected leg is commonplace, as is a period of complete immobilisation with/without a spica cast. Physiotherapists and occupational therapists will support postoperative recovery, providing wheelchairs and walking aids, adaptations for school and home environments, all individually tailored. A careful record will be made of the operative details and rehabilitation provision. The use of physiotherapy will be at the discretion of the clinical team as per their standard practice and is typically

facilitated through community physiotherapists local to the child's home. Local physiotherapists will have access to a network of study trained physiotherapists for support and families will have access to online material to facilitate post operative rehabilitation at home.

13.2 Active Containment – The Non-STOP Therapy Package (Non-Surgical Containment of Perthes' disease) (comparator/control)

Participants randomised to the active containment arm will receive a package of rehabilitation, delivered through the Non-STOP best practice therapy session.

Children and families will receive a personalised individual face-to-face best practice therapy session of up to 90 minutes with a study-trained physiotherapist at the recruiting hospital/regional specialist centre.

Children will be assessed to identify their main problems and recovery goals. They will be provided with individually tailored advice, including: a review of walking aids, reassurance, education about the condition and natural recovery process and timeframes, activity modification and exercise advice, information about use of pharmacological and non-pharmacological pain management, and what to do if they experience problems (such as flare ups of pain).

After the best practice therapy session, community physiotherapists local to the patients' home will be given access to study-trained physiotherapists at the recruiting hospital/regional specialist centre, to build a network of physiotherapy expertise in this rare disease.

Supporting materials for self-management will be provided on an online-platform and will include explainer videos and written information to guide recovery as acute pain settles and activity levels build up again. This will also be signposted on the web-platform to other places for further support from trustworthy sources, such as the STEPS charity website, which the CI and co-applicant already contribute to.

13.2.1 History of the development of the Non-STOP Therapy Package

The Non-STOP Therapy Package forms the Active Containment Intervention. Non-STOP, or the Non-Surgical Treatment of Perthes' Disease, was developed through an NIHR Fellowship by Adam Galloway (co-applicant). This was developed through a Delphi consensus process on the non-surgical management of Perthes' disease and a qualitative study [30], involving both key clinical stakeholders and children with Perthes' disease to define best practice. The development also included a systematic review of the non-surgical management of Perthes' disease and a case review of these interventions at five NHS centres [31, 32].

Interviews with children with Perthes' disease and their families emphasised the need to offer high-quality advice to support families not having surgical treatment. Parents told us they want reliable information and to be offered a credible alternative to surgery, i.e. feeling like 'something' rather than 'nothing' is being offered by the specialist centre. Traditional 'watch and wait' strategies from the specialist centre are consistently not considered acceptable by the parents and children that were consulted.

13.2.2 Training and fidelity of the Non-STOP Therapy Package

The OP Non-STOP study best practice therapy intervention will be manualised and physiotherapists delivering the intervention will be trained by the study team online and/or face-to-face.

Based on our experiences of delivering previous physiotherapy interventions, we are confident that a half to one day of training is sufficient. There will be fidelity assessments through the completion of

treatment logs by physiotherapists and observation of treatment sessions at sites by the central study research physiotherapist either in person or via audio-recordings.

13.3 Concomitant care

The interventions describe the two broad approaches to treatment which represent standard practice. No additional care, beyond standard care, is planned.

Community health professionals seeing trial participants will be made aware of the trial-trained physiotherapists with an interest in the treatment of Perthes' disease at recruiting centres to foster the development of best practice.
Families will be provided with online material to continue to facilitate their therapy at home. There will be ongoing support through the online platform and the network of therapists.

13.4 Measures to reduce the potential for cross-overs

The OP Non-STOP study team strengthened their understanding of this issue through qualitative interviews with patients, parents and clinicians [33, 34]. It is anticipated that there will be similar numbers of cross-overs in both directions.

Despite an in-depth consent discussion, after randomisation to the surgery group, some parents, in consultation with their treating clinicians, will choose not to have surgery. Likewise, other families allocated to active containment, in consultation with their treating clinicians, will choose to undergo surgery. The most appropriate course of treatment will be available for participants at all times, e.g. participants can transition between groups, or, if requested, be withdrawn from the study. We will monitor cross-overs closely (on a site-by-site basis) to identifytrends that emerge, and disseminate learning points gleaned throughout the study.

To minimise cross-overs, the OP Non-STOP study team will provide a package of information to sites, built on our learning and previous work with the QuinteT group [35], to ensure that the language clinicians use is optimised.

14 INFORMED CONSENT

14.1 Consent Procedure

If the family is interested in potentially participating in the OP Non-STOP study, they will be introduced to a member of the local study research team, and presented with the age-appropriate information materials, 'explainer video', a public website containing all relevant information and a verbal explanation of the study procedures. The family will then be given the opportunity to discuss issues related to the study with the clinical team, member of the research team, and family and friends ensuring that the potential participant and their family has sufficient time to consider participating or not. The parent will then be asked to sign an informed consent form (ICF) (only one parent will have to complete consent) and, where appropriate, children will be asked for their assent.

14.2 Time allowed to decide to take part

Participants and their families will be given as much time as they need to decide on whether to take part.

14.3 Completion of the Informed Consent Form

The potential participant, parent and the Investigator (or authorised designee) must personally sign and date the current approved version of the informed consent and assent forms as stated above.

The ICF and Assent Form will be offered to parents and potential participants in clinic/hospital as an electronic form on a tablet device (with the consent/assent forms completed directly on the study database, REDCap). Where it is not possible for a consent/assent forms to be completed in clinic (for example, if a participant has only had telephone appointments), remote electronic consent/assent may also be used.

With consent/assent forms completed electronically, signatures will be either achieved by a finger tracing across a tablet device, using an electronic stylus on a tablet device, or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen. If the parent has an email address they are willing to provide, an electronic version of the signed ICF and assent form will be automatically emailed to them. If the parent does not have/does not provide an email address the site research team will be able to print a copy of the signed ICF and assent form and provide this to the parent. A copy of the electronic consent and assent form downloaded from the study database must be placed in the eISF and a copy in the participant's medical record.

14.4 Optional aspects of consent

Participants will be required to give their consent for all aspects of study participation to take part in the study. Consent for inclusion into the NAHR for long-term follow-up however, is optional.

14.5 Individuals lacking capacity to consent

There are circumstances where the recruiting team assess that the child does not have capacity to assent, or where the situation (i.e. pain and anxiety related to the condition and surgery) means that the child expresses a wish for the decision to be made solely by their parent. Therefore, the absence of assent does not exclude the child from the study if consent has been obtained from the parent/legal representative. If a child completes the assent form indicating that they do not wish to participate, they will not be included in the study.

14.6 Participants who lose capacity during the study

In the unlikely event that the participant loses capacity to consent during the study, the parent will decide whether it is in the best interest of the child to continue taking part in the study. In the unlikely event of the parent losing capacity, other parents/guardians can complete the questionnaires, or the participant would be withdrawn from the study. If withdrawn, de-identified data already collected with consent would be retained and used in the study. No further data would be collected, or any other research procedures carried out on or in relation to the participant.

14.7 Re-consenting

Should there be any subsequent amendment to the approved protocol, which might affect a participant's participation in the study, continuing consent/assent will be obtained using an amended consent /assent form which will be signed by the parent/participant.

15 RANDOMISATION

15.1 Timing of randomisation

Randomisation will only be performed when informed consent (and assent if applicable) has been obtained and eligibility confirmed.

15.2 Randomisation procedure

Eligibility will be reconfirmed at randomisation. Participants will be randomised by the site research team via a centralised validated computer randomisation program through a secure (encrypted) web-based service, incorporated and accessed via the OP Non-STOP study REDCap database enabled by OCTRU.

The patient will be randomised at an orthopaedic clinic/hospital visit. All hospital treatment areas have access to the internet so will access the randomisation service in real time. Participants will be randomised to one of the following arms:

Table 8: Intervention and comparator

Arm	**Treatment**
Containment surgery (intervention)	Children randomised to containment surgery will receive an operation on their hip.
Active containment (comparator)	Children and families will receive an individual face-to-face best practice therapy session of up to 90 minutes with a trial-trained physiotherapist at the recruiting hospital/ regional specialist centre.

Upon randomisation of a participant, the OP Non-STOP study central team and a member of the site research team will be notified by an automated email.

Full details of the randomisation procedure will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the eTMF.

15.3 Randomisation methodology

Participants will be randomly allocated to the treatment options via automated, secure (encrypted), web-based randomisation provided by the Oxford Clinical Trials Research Unit (OCTRU) using a REDCap platform. Minimisation will be implemented with a 1:1 allocation ratio using the REDCap-Minimization module Consented participants will be allocated randomly (1:1) to either containment surgery or optimised non-surgical containment.

Randomisation will be performed using a minimisation algorithm to ensure balance between the two treatment groups using stratification factors:

- Participant age (5-7 years, 8-12 years)
- Participant sex (Male, Female)
- Degree of deformity (collapse) (>50%, exactly 50%, <50% lateral pillar height)

The first few participants will be randomised using simple randomisation, to seed the minimisation algorithm, and a non-deterministic probabilistic element will be included to prevent predictability of treatment allocation. The constraints for the randomisation schedule will be determined by the OCTRU trial statistician and full details will be detailed in the randomisation and blinding plan.

15.4 Justification for stratification factors

Stratification by age group will ensure that the treatments are balanced across age groups which may be important since older children have a worse prognosis.

Stratification by sex will ensure that the treatments are balanced across the sexes which may be important since girls have a worse prognosis.

Stratification by collapse (lateral pillar height) will ensure that the treatments are balanced across femoral head severity as more collapse has a worse prognosis.

15.5 Back-up randomisation/registration procedure

There is no back-up randomisation procedure for this study as randomisation is not time critical.

16 SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

There are currently no planned sub-studies/translational studies/mechanistic studies.

17 STUDY ASSESSMENTS/PROCEDURES AND DATA COLLECTION

The study flow chart can be found in Appendix 1 of this protocol.

17.1 Overview

Table 9 shows scheduled assessments for the study.

Table 9: Schedule of activities

Assessments	Baseline	Intervention	3 months post randomisation	6 months post randomisation	9 months post randomisation	12 months post randomisation	18 months post randomisation	24 months post randomisation	30 months post randomisation	36 months post randomisation
Demographics	*									
Status of Perthes' disease	*									
Randomisation	*									
Surgery / Best Practice Therapy Session		*								
PROMIS - Mobility	*		*	*	*	*	*	*	*	*
Wong-Baker Faces Pain Scale	*		*	*	*	*	*	*	*	*
CHU-9D	*		*	*	*	*	*	*	*	*
PROMIS - Family Relationships	*		*	*	*	*	*	*	*	*
Educational participation			*	*	*	*	*	*	*	*
Resource use Questionnaire			*	*	*	*	*	*	*	*
Complications (Additional care- participant reported)				*		*	*			*
Complications (site reported)							*			*
Collection of routinely available radiographs documenting the hip and pelvis appearance up to 36 months										*

17.2 Study questionnaires

Where possible, questionnaires will be completed electronically by the family. Families will be texted/emailed a link to complete their study questionnaires electronically. Any links to questionnaires sent to a family either by email or text is unique to a participant and their timepoint/questionnaire in the study. Telephone administered questionnaires may also be used where the use of electronic means is not possible for the family.

17.3 Data Collection

All follow-ups are collected electronically directly from the family, unless otherwise indicated.

The study will be made efficient and more environmentally friendly by ensuring that all outcomes are collected via SMS text message containing a link to an eCRF amongst those with a smart phone, an e-mail link to an eCRF for those with internet access but no smart phone, or telephone for those with no smart-phone or web-access. We have employed this technique successfully across our broad portfolio of paediatric orthopaedic trials (FORCE, SCIENCE, CRAFFT) – which included 94% primary outcome completion in the FORCE study. Trial materials will be optimised using age-appropriate multimedia resources, developed with knowledge acquired through our prior work as part of the TRECA study (NIHR HS&DR) [26]. We will ensure that all trial materials are electronic to maximize efficiency.

17.3.1 Baseline assessment

Completed at hospital by local research team member with participant/and or their parent. For a full list of data collection, please see Appendix 2.

17.3.2 Intervention

Completed at hospital by local research team member. For a full list of data collection, please see Appendix 2.

17.3.3 Follow-up assessments/subsequent visits

For a full list of data collection please see Appendix 2.

17.4 Communication with study participants by the central study team

Participants will be notified to complete study questionnaires by email or text. Participants may be sent up to two reminder messages and/or where possible may be asked to complete questionnaires during a routine clinic visit. Participants that do not complete their study questionnaires may be telephoned to collect the data or request return of the electronic questionnaire. Participants will receive an initial email/text and up to two reminder messages from a member of the central study team to collect outcome data. A welcome letter will be sent out to participants upon recruitment into the study, as well as a reminder postcard at 12, 24, and 36 months.

17.5 Qualitative assessments

No qualitative research will be performed as part of the study.

17.6 Withdrawal

Withdrawal of consent means that a participant (and/or their parent) has expressed a wish to withdraw from the study altogether or from certain aspects of the study only. The type of withdrawal will be collected on the CRF labelled ‘Withdrawal’.

The Withdrawal CRF should be completed to document the reasons for withdrawal and state who the decision to withdraw was made by. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow up any SAEs and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant/parent expresses a wish to withdraw from the study, the research team will determine which aspect(s) of the study the participant wishes to withdraw from.

The aspects of the study that the participant may request to withdraw from are as follows:

- No longer willing to complete study questionnaires but still willing to have routine data from the medical record provided to the study
- No longer willing to complete study questionnaires AND no longer willing to have routine data from the medical record provided to the study.

Where a participant/parent wishes to withdraw from all aspects of study participation, as detailed above this will be recorded on the Withdrawal CRF as full withdrawal.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from the study intervention for clinical reasons or other reasons such as non-compliance or eligibility. Participants and their parent/guardian will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the study withdrawal CRF.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the central study team. Appropriate action will be taken by the study teams (centrally and by the site research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any communications regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used/analysed as explained in the PIS.

18 BLINDING AND CODE BREAKING

18.1 Blinding

Participants and their parents cannot be blinded to their treatment. The treating clinician also cannot be blinded to the treatment they are providing. However, the clinical team will not be involved in any part of the follow-up assessment of the participants. The patient reported outcome data will be collected directly from the participants and their parents. The radiographic outcomes will be determined by an independent assessor blinded (where possible) to the interventions.

Table 10 provides an overview of the blinding status of all individuals involved in the conduct and management of the study.

Table 10: Blinding status of those involved in study conduct and management.

Role in study	Blinding status	Additional information
Participants/parents	Not blinded	It is not possible to blind due to nature of the intervention. Participants will be told their treatment allocation immediately after randomisation.

Site research staff including Principal Investigator	Not blinded	Not possible due to the nature of the intervention. Following randomisation, an email will be sent to the PI (unblinded only for participants they randomise at their own site) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation.
CI	Blinded for those at sites other than their own, except for any SAE causality assessment	The CI will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CI will become unblinded to complete the full causality assessment.
Database programmer	Not blinded	The database programmer is responsible for the management of randomisation system and the REDCap database and will have access to all unblinded datasets.
OP Non-STOP Study Management staff	Not blinded	Study Management staff within OP Non-STOP will not be blinded to treatment allocations as site staff may require support for randomisation, or participants may contact the study team directly. Serious Adverse Event reports will also be handled by the study management team which will contain allocation information.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the study randomisation system and database to ensure data quality and to undertake central monitoring activities.
Study Statistician and Senior Study Statistician	Not blinded	The study statistician and senior study statisticians will have access to treatment allocations or data needed for generating the Data and Safety Monitoring Committee (DSMC) closed reports and the final analysis. They are also unblinded as they generate the randomisation list.
Health Economist	Not blinded	The study health economist and senior health economist will have access to treatment allocations for the final analysis.
Radiographic Assessor	Blinded	Radiographs will have the shaft and neck of the femur, along with the lateral edge of the acetabulum, obscured to hide any residual changes resulting from surgery.

18.2 Code break/ unblinding

Not applicable for this study.

19 SAMPLES

This study protocol does not involve any taking of new biological samples or any use of pre-existing samples.

20 IMAGES (RADIOGRAPHS)

This study will harvest routinely collected images of the hip/ pelvis available on the PACS taken pre-operatively, post-intervention and the most recently collected at the three year post randomisation

date. These routine images will be stored in a bespoke application (TRIAGE) hosted at the University of Oxford and will be used to quantify the degree of residual deformity by an independent assessor.

21 SAFETY REPORTING

21.1 Safety reporting period

Safety reporting for each participant will begin from randomisation and will end when the participant has reached their final main follow-up time point, at 36 months post-randomisation.

21.2 Definitions

Table 11: Definitions for safety reporting

An adverse event (AE)	Any untoward occurrence in a clinical study participant. ***Note**: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the study procedures, whether or not considered related to the procedures.*
Related Adverse Event	An event that resulted from administration of any of the research procedures
Serious Adverse Event (SAE)	An AE that: • results in death • is life-threatening[1] • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator[2]
Unexpected Related Serious Adverse Event	A serious adverse event related to the study (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence).

[1] participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

21.3 Expected adverse events

This is a low risk, pragmatic trial where both of the study interventions are in common use. For this trial, foreseeable AEs will not need to be reported immediately, but will be recorded on participant and site reported CRFs. They include the following (including the need for hospital admission and/or further unplanned surgery to manage these complications in either group):

The complications anticipated in the management of these patients (particularly considering readmission or subsequent surgery) include pressure sores, non-union of the bone, wound or bone infection, major injury to nerves altering lower limb function, implant-related fracture, metalwork fracture/failure, need to remove/adjust metal implants, total hip arthroplasty (replacement).

21.4 Non-reportable AEs/SAEs

AEs that are unrelated to the intervention will not be reported. AEs deemed related to the intervention that do not meet the SAE definition and are not classed as foreseeable as per section 21.3 (such as discomfort during performance of exercises), will also not be reported.

21.5 Procedure for collecting safety events from sites/participants

These events will be recorded on patient-reported questionnaires and by the site investigators in the 'Complications' CRF if they become aware of such an event.

21.6 Reporting of SAEs from sites to the central study team

Only unexpected SAEs potentially related (possibly, probably, or definitely) to the study intervention/any of the research procedures will be reported immediately to the central study team. Such events will be reported immediately to the central study team as follows:

SAEs will be reported by the site research team using the SAE form within the REDCap study database within 24 hours of becoming aware of the event. The CTU is automatically notified of the SAE report through the database.

A paper SAE form will be used as a back-up if the SAE form is not available electronically. This must be emailed to op-nonstop@ndorms.ox.ac.uk within 24 hours of becoming aware of the event. The central study team will acknowledge receipt of any SAEs reported via email within one working day and provide the site with a unique SAE Log number.

21.7 Assessment of SAEs by the Principal Investigator (or delegate)

The PI at site (or delegated individual) is responsible for assessing all reported SAEs for seriousness, causality and expectedness.

21.7.1 Relatedness/causality

The assessment of "relatedness" to the study intervention is the responsibility of the PI at site or an agreed designee according to the following definitions:

Table 12: Relatedness of safety events

Relationship to intervention	Attribution (Causality)	Description
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

21.9 Review of SAEs by the Sponsor/CTU Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the study procedures/intervention. The site will be encouraged to respond and if a response is not provided the CI will be consulted by the CTU and the CTU will complete the Sponsor part of the SAE report.

21.10 Reporting of SAEs to the Research Ethics Committee (REC)

.All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event.

21.11 Unblinding of SAEs for reporting to the REC

PI at site not unblinded, CI to be unblinded for SAE review.

21.12 Follow-up of Serious Adverse Events

If the SAE is an unexpected related event then follow up information must be provided as requested by the central study team. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

22 PREGNANCY

If a participant becomes pregnant during their participation in the study, it does not need to be reported due to the nature of the intervention as concluded in the risk assessment of the study.

23 STATISTICAL CONSIDERATIONS

23.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP) that will be drafted early in the study and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Study Statistician in accordance with the current OCTRU SOPs. The Trial Steering Committee (TSC) and Data & Safety Monitoring Committee (DSMC) will review and, if necessary, provide input into the SAP.

23.2 Sample Size/Power calculations

172 participants providing data on the PROMIS Mobility Score for children at three years post randomisation (86 in each group) will provide 90% power to detect a difference in means of 5, assuming the standard deviation (SD) is 10 using a two group t-test with a 5% (2-sided) significance level. This is inflated to 216 participants (108 per arm) to allow for 20% attrition.

Raw scores of the PROMIS are translated into standardised T-scores with a population mean of 50 and an SD of 10.

The minimum clinically important difference (MCID) of PROMIS paediatric measures is generally 3.0-5.0 [29,30].
We discussed with children and families the size of the difference they would require to justify surgery, over optimised non-surgical containment. Given that surgery is a considerable intervention in the lives of the child and their family (i.e., the anaesthetic, the pain and scar, admission to hospital, the frequency of the requirement for a second procedure to removal metalwork, along with the lengthy

duration of immobilisation and recovery), families believed that the effect sought should be at the upper range of the MCID. Other studies have similarly highlighted that patients often seek greater effect sizes to warrant bigger surgical interventions than the established MCID [31].

23.3 Description of Statistical Methods

Reporting of results will be in accordance with the CONSORT Statement and relevant extensions [36, 37] [38].

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other validated statistical software tools.

23.3.1 Primary outcome

The PROMIS Mobility Score for Children at 3 years post-randomisation is the primary outcome of the trial. The primary analysis will use a linear regression model that adjusts for the baseline score and treatment group. As recommended by ICH E9 [39], the model will also adjust for the minimisation factors as fixed effects. An unadjusted analysis, that does not include the baseline score and minimisation factors, will also be performed.

23.3.2 Secondary outcome(s)

Continuous secondary outcomes measured over time (PROMIS Mobility over time, Wong-Baker Faces Pain Scale, CHU-9D and PROMIS Family Relationships) will be compared using a multi-level mixed effects linear regression model with repeated measures (level 1) grouped within participants (level 2). Models will include treatment, baseline score, time-by-treatment interaction and minimisation factors as fixed effects. Educational participation will be analysed as total days missed during the 3 year follow up using a Negative Binomial regression model, adjusting for treatment and minimisation factors as fixed effects. Degree of residual deformity will be analysed as Stulberg grade at 3 years follow up using an ordinal logistic regression model, adjusting for treatment and minimisation factors as fixed effects. The number and proportion of participants experiencing each type of complication will be summarised by treatment group. Heterogeneity by centre will be explored visually using forest plots and with a sensitivity analysis on the primary outcome where statistical models applied will also adjust for centre as a random effect.

23.4 Inclusion in analysis

The principal analysis will be performed on the intention to treat population, analysing participants with available outcome data in their randomised groups, regardless of adherence.

23.5 Subgroup analysis

There are no proposed subgroup analyses planned.

23.6 Interim analyses

The main outcomes will be analysed as stated in the analysis plan once the study follow-up has been completed. No formal interim analyses of treatment effect are planned for any of the study outcomes.

23.6.1 Stopping rules

As no formal interim analyses are planned, no stopping rules have been incorporated into the study design. An independent DSMC will review the accumulating data at regular intervals and may recommend pausing or stopping the study in the event of safety concerns.

23.7 Level of Statistical Significance

All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals and all tests will be carried out at a 5% two-sided significance level.

23.8 Procedure for accounting for missing data

Sensitivity analyses will explore the impact of missing data. The procedure for handling spurious or missing data will be described in the SAP. The study will attempt to collect data as completely as possible. Missing data, for example due to withdrawal, protocol deviation or patient loss to follow-up, will be summarised and patterns analysed. Analysis of the primary and all secondary outcomes will be performed using available data. If there is sufficient or differential missing data, sensitivity analyses using multiple imputation techniques will be performed. These will explore the possibility of data being missing at random as well as departures from this assumption.

23.9 Procedures for reporting any deviation(s) from the original SAP

Any deviation(s) from the original SAP will be described in the final statistical report.

23.10 Internal pilot

An internal pilot is planned that will progress seamlessly to the definitive study if predefined progression criteria are reached. Data from the internal pilot trial will contribute to the final analysis. The purpose of the internal pilot is to assess the feasibility of recruitment. Stop-go criteria (Table 13) will be reviewed at 12 months after the study opens to recruitment. The stop-go criteria are based on recruitment rate, sites open, and participants recruited. The poorest performing of the three parameters defining the action required to be taken.

Table 13: Stop-go criteria for internal pilot phase.

Progression guidance	Criteria
Continue with study – no action required	• Average recruitment rate/site/month:>0.35 • Number of sites opened: 15 • Number of participants: 50+
Continue with study – action required: • Review recruitment strategies and modify/monitor closely • Discuss strategies with the TSC and funder.	• Average recruitment rate/site/month 0.2 to 0.35 • Number of sites opened: 10-14 • Number of participants: 29-49
Review with funder	• Average recruitment rate/site/month: ≤0.2 • Number of sites opened: ≤10 • Number of participants: ≤28

The internal pilot study will mirror the procedures and logistics undertaken in the main definitive study. It is intended that the study will progress seamlessly into the main phase, with internal pilot participants included in the final analysis. Should a decision be made to stop the study, data collected would be presented to the oversight groups who, together with the funder, would decide whether participants will be followed up as per protocol.

24 HEALTH ECONOMICS

There is an integrated economic evaluation in this study, this will be informed by the NICE Reference Case [40] and reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [41].

The economic evaluation will be conducted from the perspective of the UK NHS and Personal Social Services. A participant's use of primary, secondary and community care services and medications will be collected using an electronic resource use questionnaire [42] at the timepoints listed in Table 9. The resource use questionnaire has been designed with particular note to the relevance of information and the complexity of the task. Unit costs will be applied to resource use using national reference sources.

Health states will be determined using the CHU-9D questionnaire, with utilities derived based on an age-specific valuation set QALYs will be calculated using an area under the curve approach. Missing data will be managed following best practice, and imputation will be considered to avoid the potential bias of complete case analysis. Costs and QALYs will be discounted at the recommended rate and adjusted for any baseline difference using regression models [43, 44].

The primary economic outcome will be the incremental cost-effectiveness ratio (ICER) expressed as the incremental cost per QALY gained. Uncertainty in costs and QALYs will be assessed using bootstrap credible intervals, with the probability of cost-effectiveness at different willingness to pay threshold values represented using cost-effectiveness acceptability curves.

From a broader socioeconomic perspective, out-of-pocket expenses and workdays missed by parents because of their child's condition, and time off school will be recorded and reported.

25 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the study-specific Data Management Plan. See section 29.3 or information on management of personal data.

We will ensure that trial materials are electronic to maximize efficiency. CRFs will be designed by the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Participants will be identified by a code number only. Direct access to source data/documents will be required for study-related monitoring.

All paper and electronic data will be retained for at least five years after completion of the study. Contact details will be retained until 12 months after completion of the study and consent and assent forms will be kept until the youngest participant reaches 21 years of age.

The study will be made efficient by ensuring that all outcomes are collected via hyperlink to an eCRF amongst those with a smart phone, an e-mail link to an eCRF for those with internet access but no smart phone, or telephone for those with no smart-phone or web-access.

We have employed this technique successfully across our broad portfolio of paediatric orthopaedic trials (FORCE, SCIENCE, CRAFFT) – including 94% primary outcome completion in the FORCE study. Trial materials will be optimised using age-appropriate multimedia resources, developed with knowledge acquired through our prior work as part of the TRECA study (NIHR HS&DR) [26].

25.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained.

25.2 Case report forms (CRFs)

The Investigator and study site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. Details of all protocol evaluations and investigations must be recorded in the participant's medical record for extraction onto the CRF. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent/assent form, the participant will be referred to by the study participant code number, not by name.

Source data to be recorded directly on the CRFs

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data).

25.3 Non-CRF data

All study data will be recorded on the CRF. The only additional data to be held outside of the CRF will be routinely taken redacted radiographs.

Table 14: Non-CRF data

Non-CRF data	Use of non-CRF data
Routinely taken radiographs	To be collated to then quantify the degree of residual deformity by an independent adjudication panel

25.4 Access to Data

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit study-related monitoring, audits and inspections. The data submitted by study participants directly via the study database (i.e. electronic participant reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

Members of the study team will only be able to access data that they need to, based on their roles and responsibilities within the study.

25.5 Data Recording and Record Keeping

Data will, wherever possible, be collected in electronic format with direct entry onto the study database by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford.

The database and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the study PIS.

Personal identifiable data will be kept separately from the outcome data obtained from/about the patients. Patients will be identified by a study ID only.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, research team or NHS Trust or regulatory authorities as required.

Data captured during phone calls to participants or from paper-based study questionnaires returned to the study office will be entered into the study database by suitably trained central study office staff. Full details of this process will be recorded in the Data Management Plan. Identifiable data will only be accessible by members of the research team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g., sending follow-up reminders for online form completion or telephone follow-up).

Audio recordings of treatment will be made digitally on password-protected devices. They will be stored on secure servers at the University of Oxford, identified by a trial ID and/or initials only and will only be accessible to the CI and those members of the Oxford research team who have been authorised to do so by the CI. The audio recordings will be retained for 12 months after being received and analysed as part of intervention quality assurance and then deleted. It is necessary to retain the recordings for this period as they are the source data and help us to assess treatment delivery. Access to them is required in case these are needed to refer back to these during intervention reporting.

Participants allocated to the active containment will have the option to use an App which will not collect any data, but have resources on reliable information about Perthes' disease, as well as strengthening and stretching exercises. Those in this arm will receive an email on allocation regarding the App and the creation of an account for them. Only the participants' parents email address will be shared with a third party hosting the app, and parents are given clear details of how to request the deletion of App accounts. Refer to section 29.5 for details about retention of participant identifiable data.

25.6 Electronic transfer of data

Any electronic transfer of data during the course of the study will be strictly controlled in accordance with the OCTRU SOP for Secure Information/Data Transfer.

25.7 Retention of participants

In the prior feasibility cohort (the BOSS study), the rate of outcomes through surgeon follow-up at 2-years was 92% [3]. This patient group has severe pain and severely limited quality of life; therefore, parents are generally invested in the treatment of this disease and attend follow-up. However, through the BOSS study we learned many lessons to maximise patient reported follow-up – such as managing PROM completion by the central study team, delivering questionnaires electronically (text and e-mail) and timing questionnaires with standard clinical follow-up visits (i.e., to serve as an additional contact opportunity). We will implement these strategies in this study.

Outcome responses (i.e., at all timepoints) throughout the study will be closely monitored, to identify and overcome any specific concerns or barriers with individual participants that may arise.

26 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The study management group will be responsible for ensuring adherence to the study protocols at the study sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. The OCTRU has a QA team who will monitor this study by conducting audits of the TMF. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the central CTU study team Additionally, the study may be monitored, or audited by Sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

A study-specific data management and monitoring plan will be in place prior to the start of the study.

26.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the study opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the study or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

26.2 Study monitoring

Monitoring will be performed by the central study team according to a study-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The CRF data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner (within no more than 14 working days of the data query unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution.

Study sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the study. Central study team staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in accordance with OCTRU SOPs and the study monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

Intervention delivery will be monitored periodically to ensure fidelity. Site visits will be conducted. Permission will be sought from the trial participants to observe or record treatment sessions. Verbal consent will be provided and recorded.

CRFs will also be used to monitor intervention fidelity. Data will be collected on intervention content delivery and number of treatment sessions attended to facilitate monitoring and reporting. The sites will regularly receive feedback from quality activities to help maintain and improve fidelity.

26.3 Audit and regulatory inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit visit. Anyone receiving notification of an audit that will (or is likely to) involve this study must inform the Central study team without delay.

26.4 Study committees

26.4.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established for the study and operate in accordance with a study-specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities/ individuals will be invited as required for specific items/issues.

26.4.2 Data and Safety Monitoring Committee (DSMC)

An independent DSMC will be established for this study. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the study. The DSMC will meet regularly throughout the study at time-points agreed by the Chair of the Committee and the CI. At a minimum this will be on an annual basis. The DSMC will review the safety data generated, including all safety data and make recommendations as to whether the protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

26.4.3 Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. The TSC will act in accordance with a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the study towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the study

The TSC will consider, and act, as appropriate, upon the recommendations of the DSMC.

27 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

27.1 Identification of recruitment sites

Recruitment sites will be selected based on their suitability to conduct the study. Potential sites will be invited to complete a site feasibility questionnaire (SFQ) which will be used by the TMG to assess

the suitability of the site for the study; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

27.2 Study site responsibilities

The PI or lead clinician for the study site has overall responsibility for the conduct of the study but may delegate responsibility where appropriate to suitably experienced and trained members of the site research team. All members of the site research team must complete the delegation log provided by the central study team prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on delegated responsibilities.

27.3 Study site set up and activation

The PI leading the participating study site is responsible for providing all required core documentation. Mandatory site training which is organised by the central study team (see below) must be completed before the site can be activated. Training in the study processes will be administered at site initiation visits delivered either in person or online by the central study team. The central study team will check to confirm that the site has all the required study information/ documentation and is ready to recruit. The site will then be notified once they are activated on the study database and are able to begin recruiting participants.

Following the pilot phase, the main recruitment phase will continue for an additional 18 months (total 30 months recruitment). During the first 6 months of the main phase, staggered opening of additional sites will take place. It is expected that the trial will eventually recruit from a minimum of 28 centres across the UK.

27.4 Training

Training in the study processes will be administered at site initiation visits (delivered face to face or online) online by the central CTU study team.

27.5 Study documentation

The central study team will provide an electronic Investigator Site File (ISF) to each participating site containing the documents needed to conduct the study. The central study team must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the study, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the study.

28 ETHICAL AND REGULATORY CONSIDERATIONS

28.1 Summary of study-specific considerations

The major barrier is the willingness of clinicians and families to be involved in a study comparing surgery vs. no surgery. The OP Non-STOP team have gradually built up our clinician collaborative over the past 6 years to initially deliver observational studies (BOSS), then randomise to relatively simple interventions (FORCE), to randomising to more challenging interventions (SCIENCE, CRAFFT). Alongside the trials, we have delivered qualitative research that has informed the team and our wider trials group about the perception of families to uncertainty, and taught us how to approach this.

Members of the OP Non-STOP team have also delivered a QuinteT training day amongst the trials group, to consider how we best present research to families. Our work to date has therefore built gradually up to this study, which is undoubtedly one of the more challenging, though desperately

needed trials in children's orthopaedic surgery. Alongside the clinician group, we have brought together an interested disease-focused patient group who are keen to engage in the delivery of the research.

28.2 Declaration of Helsinki

The Investigator will ensure that the study is conducted in accordance with the principles of the Declaration of Helsinki.

28.3 Guidelines for Good Clinical Practice

The Investigator will ensure that the study is conducted in accordance with relevant regulations and with the principles of GCP.

28.4 Ethical conduct of the study and ethical approvals

The protocol, patient information sheet, ICF and any other information that will be presented to potential study participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent REC.

28.5 NHS Research Governance

Once HRA & Health and Care Research Wales (HCRW) approval is in place for the study, sites will confirm capability and capacity to participate in the study.

28.6 Protocol amendments

All amendments will be generated and managed according to the OCTRU SOPs to ensure compliance with applicable regulations and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators as applicable for the amendment type. The only exceptions are for changes necessary to eliminate an immediate hazard to study participants (see below).

It is the Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information becomes available that might affect the participant's willingness to continue in the study. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

28.7 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A study related deviation is a departure from the ethically approved study protocol or other study document or process or from GCP or any applicable regulatory requirements. Deviations from the protocol will be captured within the study database either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from the study database and reviewed regularly by the TMG. Deviations will be handled and reviewed in a timely manner in accordance with a study-specific Data Management and Monitoring Plan.

The investigator must promptly report any important deviation from GCP or protocol to the central study team. Examples of important deviations are those that might impact patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP.

28.8 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The study may continue with the urgent safety measures in place.

The Investigator must inform the central study team IMMEDIATELY if the study site initiates an urgent safety measure:
The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the central study team to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The central study team will follow written procedures to implement the changes accordingly.

28.9 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods *or* to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of participants already in the study for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the study in a timely manner.

The central study team will report the temporary halt via an expedited substantial amendment procedure.
The study may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the study this will be reported as an early termination.

28.10 Serious Breaches

A “serious breach” is a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the study subjects; or
(b) the scientific value of the research.

Investigators must notify the central study team within one working day if any serious breach of GCP is suspected. The central study team will review the event and, if appropriate will report a serious breach to the sponsor, the REC and the NHS host organisation within 7 days of the central study team becoming aware of the breach.

28.11 Study Reports

This protocol will comply with all current applicable REC and Sponsor reporting requirements.

28.12 Transparency in Research

Prior to the recruitment of the first participant, the study will be registered on a publicly accessible database ISRCTN83315571), which will be kept up to date during the study, and results will be uploaded to the registry within 12 months of the end of the study declaration. A Final Report will be submitted to the REC containing a lay summary of the study results which will be published on the HRA website.

The results of the study will be published and disseminated in accordance with the section 34.

28.13 Use of social media

Social media (e.g. Twitter feeds) may be utilised to make general announcements about the study and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment at a site etc).

29 PARTICIPANT CONFIDENTIALITY

29.1 Collection and use of personal identifiable information

Contact details (*e.g. e-mail addresses/postal addresses/phone number)* for parents (as well as children and a secondary contact, if consent given)) will be collected in this study for the following purposes, and where an activity is optional, only with the specific consent of the participant:

- Sending of follow-up questionnaires and any reminder messages
- Sending text messages regarding follow-up questionnaires
- Sending a copy of the completed consent form by email (for any participants that consent electronically and wish to receive a copy by email)
- Sending of Welcome pack/reminder postcards direct to participant's homes
- Collection of (NHS/CHI/H&C number)
- Contact with regards to long term follow up

The patient information sheet explains what contact details will be collected and how these will be used.

Where remote eConsent is used, participants will be asked to give their permission verbally for a link to the consent documentation to be sent to their email address or an email address they provide.

29.2 Use of audio /visual recording devices

If necessary audio recordings of interventions will be conducted. Permission will be sought, and verbal consent recorded, from the trial participants to record treatment sessions. Audio recorders will be sent from the site to the trial team via recorded delivery.

29.3 Storage and use of personal data

During the study personal data will be stored and used in accordance with the OCTRU SOP for confidentiality, protection and breach of personal data in relation to research subjects. This ensures that all personal data collected during the study is recorded, handled and stored in accordance with the requirements of the UK General Data Protection Regulation.

All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal

data of participants will be minimised wherever possible by the use of a unique participant study number on study documents and any electronic databases.

Personal data on all documents will be regarded as confidential. The study staff will safeguard the privacy of participant's personal data.

The use of all personal data in the study will be documented in a study-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

The investigating sites will maintain the patient's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

29.4 Access to participants' personal identifiable data during the study

Access to participants personal identifiable data will be restricted to individuals authorised to have access. This includes a) members of the research team at participating study sites with delegated responsibility by the site PI and b) members of the central study team involved in the conduct/management of the study where this is necessary for their role.

Research staff that are not part of the potential participant's direct healthcare team will not have access to personal identifiable data until the individual has given their consent to take part in the study or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site research team – permission for this will be recorded in the individual's medical notes.

The participant information sheet clearly describes who will have access to the participants' personal identifiable data during the study.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the study being looked at by individuals from the Alder Hey NHS Trust, University of Oxford, University of Liverpool and Bangor University, from regulatory authorities and from the NHS Trust(s), where it is relevant to their taking part in this trial; only authorised individuals will be granted access where this is necessary for their role.

29.5 Destruction of personal identifiable data

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the study data management plan and is in accordance with OCTRU standard operating procedures which comply with the UK GDPR.

29.6 Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the ISF and are not to be released externally.

30 PUBLIC AND PATIENT INVOLVEMENT

30.1 PPI in study design and protocol development

This study is a partnership with affected families that was developed over six years. The OP Non-STOP team held multiple family workshops, both in person and on zoom, and attended 'activity camps' for children to understand the impact of disease, discuss the role of research and the direction that research should take. There were 125 families who contacted members of the research team to support the development of research and a smaller group of eight families with whom we regularly consult.

The families affected by Perthes' disease have been instrumental in highlighting the importance of the disease through their involvement in the James Lind Alliance process [13]. Working as partners the core outcome set for Perthes' Disease was developed, with families acting as both participants in the Delphi study and members of the steering group [11]. PPI participated in the oversight of the BOSS Study for over 5 years – which formed much of the basis for this study [45]. Families have also been instrumental in developing the package of 'optimised non-surgical containment', named by them as the Non-STOP package (Non-Surgical Treatment of Perthes' disease) – which has a logo designed by children. The logo has subsequently been adapted for this trial

A group of children and families affected by Perthes' disease influenced the study design and participated in its development.

30.2 PPI during the study

Parents and Children of the NIHR GenerationR Young Persons Advisory Group (YPAG) will be involved throughout the study, in a similar manner to they were in the BOSS study and other trials by:
(a) informing the development of patient facing documents,
(b) overseeing professional designers to produce appealing materials
(c) advising on the content of an explainer animations and web content

The YPAG will be kept abreast of study progress through regular updates and will advise on the content and format of dissemination materials.

30.3 Dissemination of study results

Findings of the study will be made available to participants via the study website and social media.

We will prepare an appealing and accessible trial website to house dissemination materials to professionals, trial participants and their families and the public in a single place. Finally, we will ensure we update the Wikipedia page for "Perthes' disease" to include details of the study result.

31 EXPENSES/PAYMENTS TO PARTICIPANTS

Participants have the option to claim a £10 voucher after each annual follow-up is completed. This is to recompense families for any out-of-pocket expenses in relation to data completion. If participants accept this voucher it will be sent automatically as an e-voucher following the questionnaire completion. This will be 'offered' as some families in the study's development have indicated that they would prefer not to accept such money 'from the NHS'.

32 SPONSORSHIP, FINANCE AND INSURANCE

32.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

32.2 Funding and support in kind

The table below provides a summary of all funding and support in kind for the study.

Table 15: Funding

Funder	Financial and non-financial support given
NIHR – HTA programme	Reference Number: NIHR152309

32.3 Insurance

Alder Hey Children's NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to participants treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

33 CONTRACTUAL ARRANGEMENTS

Appropriate contractual arrangements will be put in place with all third parties.

This study is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the study as appropriate.

34 PUBLICATION AND DISSEMINATION

The Sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results will be in accordance with OCTRU SOPs and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/) [46]. The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research at the completion of the study, after all participants have undergone 3 years of follow-up and data analysis has been performed. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) [36] including any applicable extensions to this. The Template for Intervention Description & Replication (TIDieR) [47] statement will be used for reporting the intervention.

The statistical and health analysis plan will be published in an open-access format before recruitment is completed.

34.1 Study results

All data will be presented such that no individual participants can be identified.

34.2 Dissemination of study results to participants

A summary of the study results for study participants will be written collaboratively with clinicians and patient representatives and distributed accordingly. The Participant Information Sheet (PIS) includes a link to the study website where participants will be advised that the results will be published. Newsletters, Facebook, Twitter etc. will also be used to ensure the results of the study are communicated to the wider community once they are available.

Dissemination of results will include the following methods:

Conference: The results of this study will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders (Orthopaedic surgeons, orthopaedic nurse practitioners and trainees in orthopaedic surgery).

Publications: Results will usually be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper, along with links to other digital media on the study website to explain the study result in an accessible format – i.e. an explainer video and infographic.

Public Dissemination: To ensure a broad campaign we will use the plain English summary and digital media communicating the study result to target a range of social media outlets (this may include an explainer video and infographic) e.g. Twitter and online sites such as STEPS Worldwide patient charity. We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal' and other professional journals (e.g. Pulse, Health Service Journal, Nursing Times). An appealing and accessible trial website will be constructed to house dissemination materials to professionals, trial participants and their families and the public in a single place.

The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. Moreover, the University of Liverpool, University of Oxford, and Alder Hey Children's' Hospital NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, will enable agreement upon effective communication strategies including co-ordinated press releases, interviews etc.

34.3 Authorship

Authorship of any publications arising from the study will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this study must acknowledge the contribution of participants, funder(s), OCTRU, Oxford Trauma and Emergency Care and the Sponsor.

35 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Ownership of IP generated by employees of the Alder Hey Hospital vests in Alder Hey Hospital. The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at Alder Hey Hospital unless it is generated in collaboration with the University of Oxford in which case this is led by the University's technology transfer office, Oxford University Innovations.

36 ARCHIVING

36.1 Minimum Mandatory archiving period

Investigators may not archive or destroy essential study documents or samples without written instruction from the central CTU study team.

The minimum mandatory archiving period for essential study documents for this study is 3 years after the youngest participant reaches 18 years old, or 5 years after the end of study, whichever is longer.

36.2 Archiving responsibilities/procedure

During the study and after study closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical study and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period as specified above.

36.2.1 Trial Master File

All paper and electronic data including the TMF and study database will be retained and archived in accordance with OCTRUs SOPs which are compliant with the UK GDPR.

36.2.2 Investigator Site File and participant medical records

The ISF will be archived at the participating site. The medical files of study participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period of time permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the trial Sponsor.

36.3 Retention of data sets

Study data and associated metadata electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

37 DATA SHARING

The study statistician and health economist may retain copies of anonymised datasets for the purpose of data sharing in accordance with the study data sharing plan.

37.1 Retention of anonymised datasets

Upon completion of the study, anonymised research data may be shared with other organisations on request to the CI and in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s).

38 REFERENCES

1. Perry, D.C., P.J. Skellorn, and C.E. Bruce, *The lognormal age of onset distribution in Perthes' disease: an analysis from a large well-defined cohort.* Bone Joint J, 2016. **98-B**(5): p. 710-4.
2. Perry, D.C., et al., *Perthes' disease: deprivation and decline.* Arch Dis Child, 2011. **96**(12): p. 1124-8.
3. Perry, D.C., et al., *The British Orthopaedic Surgery Surveillance study: Perthes' disease: the epidemiology and two-year outcomes from a prospective cohort in Great Britain.* Bone Joint J, 2022. **104-B**(4): p. 510-518.
4. Metcalfe, D., et al., *Temporal trends and survivorship of total hip arthroplasty in very young patients: a study using the National Joint Registry data set.* Bone Joint J, 2018. **100-B**(10): p. 1320-1329.
5. Hall, A.J., et al., *Perthes' disease of the hip in Liverpool.* Br Med J (Clin Res Ed), 1983. **287**(6407): p. 1757-9.
6. Perry, D.C., et al., *Legg-Calve-Perthes disease in the UK: geographic and temporal trends in incidence reflecting differences in degree of deprivation in childhood.* Arthritis Rheum, 2012. **64**(5): p. 1673-9.
7. Perry, D.C., et al., *Perthes' disease of the hip: socioeconomic inequalities and the urban environment.* Arch Dis Child, 2012. **97**(12): p. 1053-7.
8. Wiig, O., T. Terjesen, and S. Svenningsen, *Prognostic factors and outcome of treatment in Perthes' disease: a prospective study of 368 patients with five-year follow-up.* J Bone Joint Surg Br, 2008. **90**(10): p. 1364-71.
9. Herring, J.A., H.T. Kim, and R. Browne, *Legg-Calve-Perthes disease. Part I: Classification of radiographs with use of the modified lateral pillar and Stulberg classifications.* J Bone Joint Surg Am, 2004. **86**(10): p. 2103-20.
10. Leo, D.G., et al., *Perspectives on the Social, Physical, and Emotional Impact of Living With Perthes' Disease in Children and Their Family: A Mixed Methods Study.* Glob Pediatr Health, 2019. **6**: p. 2333794X19835235.
11. Leo, D.G., et al., *The outcomes of Perthes' disease.* Bone Joint J, 2020. **102-B**(5): p. 611-617.
12. Perry, D.C., et al., *A consensus exercise identifying priorities for research into clinical effectiveness among children's orthopaedic surgeons in the United Kingdom.* Bone Joint J, 2018. **100-B**(5): p. 680-684.
13. Vella-Baldacchino, M., et al., *Research priorities in children requiring elective surgery for conditions affecting the lower limbs: a James Lind Alliance Priority Setting Partnership.* BMJ Open, 2019. **9**(12): p. e033233.
14. Marson, B.A., et al., *Quality of patient-reported outcomes used for quality of life, physical function, and functional capacity in trials of childhood fractures.* Bone Joint J, 2020. **102-B**(12): p. 1599-1607.
15. Achten, J., et al., *A multicentre prospective randomized equivalence trial of a soft bandage and immediate discharge versus current treatment with rigid immobilization for torus fractures of the distal radius in children: protocol for the Forearm Fracture Recovery in Children Evaluation (FORCE) trial.* Bone Jt Open, 2020. **1**(6): p. 214-221.
16. Varni, J.W., et al., *PROMIS(R) Parent Proxy Report Scales: an item response theory analysis of the parent proxy report item banks.* Qual Life Res, 2012. **21**(7): p. 1223-40.
17. Varni, J.W., et al., *PROMIS(R) Parent Proxy Report Scales for children ages 5-7 years: an item response theory analysis of differential item functioning across age groups.* Qual Life Res, 2014. **23**(1): p. 349-61.
18. Segawa, E., B. Schalet, and D. Cella, *A comparison of computer adaptive tests (CATs) and short forms in terms of accuracy and number of items administrated using PROMIS profile.* Qual Life Res, 2020. **29**(1): p. 213-221.
19. Leo, D.G., et al., *PROMIS Paediatric Mobility tool is correlated with accelerometer-measured physical activity in children with hip diseases.* Bone Joint J, 2021. **103-B**(2): p. 405-410.

20. Wong, D.L. and C.M. Baker, *Pain in children: comparison of assessment scales.* Pediatr Nurs, 1988. **14**(1): p. 9-17.
21. Garra, G., et al., *Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients.* Acad Emerg Med, 2010. **17**(1): p. 50-4.
22. Shields, B.J., et al., *Pediatric pain measurement using a visual analogue scale: a comparison of two teaching methods.* Clin Pediatr (Phila), 2003. **42**(3): p. 227-34.
23. Perry, D.C., et al., *Immobilisation of torus fractures of the wrist in children (FORCE): a randomised controlled equivalence trial in the UK.* Lancet, 2022. **400**(10345): p. 39-47.
24. Stevens, K., *Valuation of the Child Health Utility 9D Index.* Pharmacoeconomics, 2012. **30**(8): p. 729-47.
25. Bevans, K.B., et al., *Children's family experiences: development of the PROMIS((R)) pediatric family relationships measures.* Qual Life Res, 2017. **26**(11): p. 3011-3023.
26. Moe-Byrne, T., et al., *Does digital, multimedia information increase recruitment and retention in a children's wrist fracture treatment trial, and what do people think of it? A randomised controlled Study Within A Trial (SWAT).* BMJ Open, 2022. **12**(7): p. e057508.
27. Bower, P., et al., *Is health research undertaken where the burden of disease is greatest? Observational study of geographical inequalities in recruitment to research in England 2013-2018.* BMC Med, 2020. **18**(1): p. 133.
28. Bowyer, G.G., A; Nielsen, A, *Closing the Digital Divide for Good*. 2021.
29. Ofcom, *Children and parents: media use and attitudes report 2022*. 2022.
30. Galloway, A.M., et al., *"Waiting for the best day of your life". A qualitative interview study of patients' and clinicians' experiences of Perthes' disease.* Bone Jt Open, 2023. **4**(10): p. 735-741.
31. Galloway, A.M., et al., *A systematic review of the non-surgical treatment of Perthes' disease.* Bone Jt Open, 2020. **1**(12): p. 720-730.
32. Galloway, A.M., et al., *A case review to describe variation in care following diagnosis of Perthes' disease.* Bone Jt Open, 2020. **1**(11): p. 691-695.
33. Papiez, K., et al., *A qualitative study of parents' and their child's experience of a medial epicondyle fracture.* Bone Jt Open, 2021. **2**(6): p. 359-364.
34. Phelps, E.E., et al., *Protecting my injured child: a qualitative study of parents' experience of caring for a child with a displaced distal radius fracture.* BMC Pediatr, 2022. **22**(1): p. 270.
35. 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.
36. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
37. Boutron, I., et al., *Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration.* Ann Intern Med, 2008. **148**(4): p. 295-309.
38. Calvert, M., et al., *Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension.* JAMA, 2013. **309**(8): p. 814-22.
39. *ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group.* Stat Med, 1999. **18**(15): p. 1905-42.
40. NICE, *NICE health technology evaluations: the manual*, NICE, Editor. 2022: London.
41. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations.* BMJ, 2022. **376**: p. e067975.
42. Measurement, D.o.I.f.R.U. *DIRUM: Home* 2023 [cited 2023 27 July]; Available from: http://www.dirum.org/.

43. Manca, A., N. Hawkins, and M.J. Sculpher, *Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility.* Health Econ, 2005. **14**(5): p. 487-96.
44. Mihaylova, B., et al., *Review of statistical methods for analysing healthcare resources and costs.* Health Econ, 2011. **20**(8): p. 897-916.
45. Perry, D.C., et al., *The BOSS Study. Determining the incidence and clinical outcomes of uncommon conditions and events in orthopaedic surgery.* Bone Jt Open, 2020. **1**(3): p. 41-46.
46. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
47. Hoffmann, T.C., et al., *Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide.* BMJ, 2014. **348**: p. g1687.

39 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

Table 16: Version history

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the protocol
2.0	TBC	Minor changes following funder and REC review. - Ensuring clarity around participants being able to change treatment when needed - Administrative updates (ISRCTN number added, names deleted) - Clarification of stop/go criteria - Clarification of use of paper data collection forms - Ensuring questionnaires per time points align across protocol

APPENDIX 1 – STUDY FLOW CHART

Sites screen out-patients clinics/acute hospital admissions. Identify potential participants:

- Children aged 5-12
- Perthes' disease
- Willing and able to give informed consent/assent

Potential participants approached about study in routine out-patient clinic visits; or acute hospital admissions by the clinical care team who if the patient and their family is potentially interested in finding out more about the study verbally agrees for their details to passed onto members of the local Op Non-STOP research team.

Potential participants contacted by clinical team in person – present the study participant information sheet and links to the study explainer video and infographic explaining the study can be accessed

Baseline visit: eligibility checked, consent/assent sought, demographic and Perthes history collected and participant reported questionnaire

For those approached in clinic this eligibility review and seeking of consent/assent may be on the same day or arranged for another day

Baseline data collection complete

- Exclusion criteria cross-checked
- Randomised

Containment Surgery (n=108)	Best Practice Advice (n=108)
3 Month	3 Month
6 Month	6 Month
9 Month	9 Month
12 Month	12 Month
18 Month	18 Month
24 Month	24 Month
30 Month	30 Month
36 Month	36 Month

Intervention assigned aimed to be delivered within 3 months

Data collection at

Data collection at

Site checks made at 18 and 36 months regarding safety and at 36 months sends any routinely collected X-rays to the Op Non-STOP study team

APPENDIX 2 – DATA COLLECTION

Baseline:

Sourced/Collected by Local Research Team in a clinic visit

- Date of baseline visit
- Participant demographics
    - Ethnicity
    - Biological sex
    - Index of Multiple Deprivation
- Perthes' disease at diagnosis
    - Affected hips (unilateral, bilateral)
    - Current disease stage by radiological status
        - Waldenström classification (0,1A,1B,2A,2B,3A,3B,4)
        - Documented stiffness (stiff, minimal/no stiffness)
        - Degree of deformity (collapse) (>50%, exactly 50%, <50% lateral pillar height)

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - PROMIS Pediatric Family Relationships Questionnaire

Intervention

Surgery

Sourced/Collected by Local Research Team in post-operative period.

- Date of surgery
- Grade of surgeon performing the operation
- Operation type (Varus osteotomy, shelf osteotomy, Salter osteotomy, other redirectional acetabular osteotomy, soft tissue surgery)
- Core decompression performed? (Yes/No)
- Hip distraction performed? (Yes/No)
- Intra-operative complications
- Post-Operative Instructions (Spica/ cast - Yes (Duration?)/ No)

Best practice therapy session

Sourced/Collected by Local Research Team in a clinic visit

- Date of session
- Name of physiotherapist delivering session
- Length of session (minutes)
- Content of session included:
    - Individually tailored advice? (Yes/No)
    - Review of walking aids? (Yes/No)
    - Walking aids given (yes/no, if yes what?)

- Reassurance? (Yes/No)
- Education about the condition? (Yes/No)
- Activity modification? (Yes/No)
- Exercise advice? (Yes/No)
- Pain management information? (Yes/No)
- Goal setting (yes/no)
- What to do if they experience problems? (Yes/No)
    - Any option above if select 'no', will prompt 'Why?'

3 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

6 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Complications
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

9 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function

    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

12 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Complications
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

18 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date
- Complications

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Complications
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

24 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

30 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire

36 months post randomisation

Sourced/Collected by Local Research Team in a clinic visit / telephone call

- Date
- Complications/SAE review
- All radiographic images collected as part of routine practice will be harvested and given to the study team. In particular, images taken pre-operatively, post-intervention and as close as possible to the 3 year post intervention date will be collated.

Direct Participant Report (collected electronically)

- Patient assessment of function
    - PROMIS Mobility CAT
- Pain
    - Wong-Baker FACES Pain Scale
- Quality of life
    - CHU-9D
- Impact of the condition
    - Resource use
    - Complications
    - Participation in Education
    - PROMIS Pediatric Family Relationships Questionnaire