CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

FULL STUDY TITLE: ODD SOCKS - Outcomes of Displaced Distal tibial fractures - Surgery Or Casts in KidS: A multi-centre prospective randomised superiority trial of conservative versus surgical treatment for displaced distal tibial fractures in children

SHORT STUDY TITLE: ODD SOCKS - Outcomes of Displaced Distal tibial fractures - Surgery Or Casts in KidS

STUDY ACRONYM: ODD SOCKS

Version: 3.0 15Feb2024

Study website: www.ODDSocks.org

Confidentiality Statement

In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all.

Contents

1 RESEARCH REFERENCE NUMBERS

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Funder Reference(s):	NIHR132675
Ethics Reference Number:	24/EM/0006
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Registry:	International Standard Randomised Controlled Trial Number (ISRCTN): 16320803
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2 ORGANISATIONAL INFORMATION.

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Sponsor:	Alder Hey Children's NHS Foundation Trust Refer to the KEY STUDY CONTACTS section for contact details.
Clinical Trials Unit:	The study is managed by Oxford Trauma and Emergency Care (OTEC). Oxford Clinical Trials Research Unit (OCTRU) Botnar Research Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LF.
Funder:	The study is funded by National Institute for Health Research (NIHR). Refer to 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: **Professor Dan Perry (Co Chief Investigator)** Consultant Children's Orthopaedic Surgeon University of Liverpool ✉DanPerry@liverpool.ac.uk **Mr Ben Marson** ST8 T&O University of Nottingham ✉Ben.Marson@nottingham.ac.uk **Dr Catrin Plumpton** Health Economist Bangor University ✉ c.o.plumpton@bangor.ac.uk **Dr Stuart Hartshorn** Consultant in Paediatric Emergency Medicine Birmingham Women's and Children's NHS Foundation Trust ✉stuart.hartshorn@nhs.net **Dr David Keene** Physiotherapist and NIHR Post Doc Fellow University of Exeter ✉ d.keene@exeter.ac.uk **Mr Nicolas Nicolau**

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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 published and made freely and openly accessible to all.

3 KEY STUDY CONTACTS

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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 Oxford Clinical Research Trials 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

Why this research?

Broken ankles in children often involve the area from which the bone grows – the growth plate. Following growth plate injuries, the growth of the main shin bone in the lower leg (the tibia) can be altered permanently, which can cause the bone to not grow at all, or to grow wonky. Altered growth may have an effect on how well the leg works. The younger the child at the time of injury (i.e. the more they have to grow), the worse the problem may become once the child has fully grown. There are different ways to treat this injury, but it is currently unclear whether one type of treatment is better than another.

Some doctors believe that children with growth plate injuries need surgery to reset the bones to ensure that the growth plate is restored into its original position. They believe that this will lower the chance of abnormal growth. However, other doctors believe that attempting to reset the bones to restore the growth plate with surgery could bring about further damage. These doctors recommend the bones to be treated in a plaster cast, without surgery to reset the bones.

What is the question being asked?

When children between 8 and 15 years old break their ankles, does surgery to reset the bones lead to better function than letting the bones heal using a plaster cast without resetting the bones?

What sort of study is it?

This study is called a trial, which is the best and fairest way to compare treatments. In the Outcomes of Displaced Distal tibial fractures - Surgery Or Casts in KidS (ODD SOCKS) Study, half the children and young people will have their broken bones treated with surgery, whilst the other half will have a plaster cast with no surgery.

How many children will be involved?

We plan to include at least 192 children over a three-year period from approximately 30 hospitals in the UK. This participant number is calculated based on previous scientific research to ensure that the study is large enough to reach a firm conclusion.

What will families be asked?

Children will be asked to join the study if they are between 8 and 15 years old and have a fracture through the growth plate at the bottom of the shin bone, where the bone ends have moved apart from each other.

Those who agree to join the study, with the support of their families, will be split fairly into two groups, using a research process called ‘randomisation’. Children will be assigned one of two treatments:

1. SURGICAL REDUCTION – the children in this group will have an anaesthetic or be sedated so their bones can be reset in theatre, and a plaster cast put on their leg. Sometimes, if the doctor thinks it necessary, wires, screws or a plate and screws will be inserted to hold the broken bones in position.

2. CONSERVATIVE TREATMENT – the children in this group will not have the bones reset in position, they will receive a plaster cast for support to allow the bones to heal naturally.

The plaster casts will stay on for around 4-6 weeks for both treatments.

All children will be followed-up for two years to keep track of their function, and the length and appearance of the leg. They will be asked about pain, whether they needed any more surgery, school attendance, complications, the number of hospital visits, their quality of life and satisfaction with treatment.

We will also record the child's NHS number (or CHI number in Scotland or H&C (Health & Care) number in Northern Ireland), to look at NHS records in the future to see if they had any future problems with their ankle. This part of the study is dependent on further funding and ethical approval.

How will this research make a difference?

At the end of the study, we will combine the information about all the children that took part. This will help everyone to know what the best treatment is. To make sure people learn about the best treatment, the doctors who help with this study will talk to other doctors, and other people in the NHS who write national guidelines. Our patient co-investigators will help deliver the message to families and will be invited to share their experience of the study with medical professionals.

6 STUDY SYNOPSIS

Full Study Title:	ODD SOCKS - Outcomes of Displaced Distal tibial fractures - Surgery Or Casts in KidS: A multi-centre prospective randomised superiority trial of conservative versus surgical treatment for displaced distal tibial fractures in children	
Short Title:	ODD SOCKS - Outcomes of Displaced Distal tibial fractures - Surgery Or Casts in KidS	
Study Acronym:	ODD SOCKS	
Study Design:	The ODD SOCKS study is a multi-centre prospective, superiority, randomised controlled clinical study.	
Study Aim	The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost-effectiveness of surgical reduction, compared to conservative treatment, for the management of displaced Salter Harris-II fractures of the distal tibial physis in children.	
Study Participants/ Target Population:	The ODD SOCKS study will recruit children aged 8-15 years with a displaced extra-articular fracture of the distal tibia involving the physis and metaphysis. Refer to section 11 of the main body of the protocol for full eligibility criteria	
No. of study arms:	Two	
Intervention(s):	Surgical reduction	
Comparator:	Conservative treatment	
Planned Sample Size:	A minimum of 192 patients.	
Target no. of research sites:	30	
Countries of recruitment:	UK	
Planned recruitment duration:	Recruitment is expected to last for 33 months.	
Duration of intervention/treatment:	4-6 weeks	
Follow-up duration:	Each participant will be followed up for 24 months from randomisation.	
Primary objective and outcome measure:	**Objective** To determine whether children treated with surgical correction have improved function	**Outcome Measure** PROMIS-Mobility

	compared with children treated with conservative care, as measured by the *Patient Reported Outcomes Measurement Information System (PROMIS) Mobility Score for Children* at two years post-randomisation.	
Additional objectives and outcome measures:	Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main body of the protocol for full study objectives and outcome measures.	

7 ABBREVIATIONS

AE	Adverse Event
BSCOS	British Society Of Children's Orthopaedic Surgery
CAT	Computer Adaptive Test
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
EQ-5D-Y	EuroQol – youth
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
H&C	Health & Care Number (Northern Ireland)
HRA	Health Research Authority
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention-To-Treat
MCID	Minimal Clinically Important Difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
OTEC	Oxford Trauma and Emergency Care
PAG	Parents Advisory Group
PI	Principal Investigator
PIS	Patient information sheet
PPC	Premature Physeal Closure
PPI	Patient and Public Involvement
PROMIS	Patient Report Outcomes Measurement Information System
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
YPAG	Young Persons Advisory Group

8 BACKGROUND INFORMATION AND RATIONALE

In the UK there are 250,000 fractures in children each year, with one third of children sustaining a fracture in childhood [1]. Fractures in children can be complicated by the involvement of a growth plate (physis) which, if damaged, can potentially affect future growth. Ankle fractures are among the most common cause of growth plate injuries in children, second only to distal radius fractures [2]. It is at these growth plates that longitudinal growth of the leg occurs (i.e. growth contributing to height). Children are prone to injuries of the growth plate because these are the weakest part of the skeleton in children, and therefore injuries that typically cause a sprain in adults tend to cause a growth plate fracture in children [3].

The growth plate at the distal tibia contributes approximately 3-5mm of length to the leg per year during childhood, accounting for 45% of tibial growth and 20% of overall leg length [4,5]. If this growth plate is damaged during a fracture, it may heal with a solid block of bone from which no growth can occur. This process is known as Premature Physeal Closure (PPC). In its simplest form, PPC may stop all growth at the growth plate, causing a difference in the length of the leg compared to the unaffected side. However, if just part of the growth plate is damaged, then PPC may occur in only part of the bone. With partial PPC, growth ceases in the damaged portion of the growth plate but continues in normal elements of the growth plate. This can lead to the bone progressively angulating as the child grows [6–10]. The younger the child at the time of injury (i.e. the more growth remaining), the worse the eventual degree of deformity at maturity. Growth in children tends to cease at 14 years in girls and 16 years in boys, so an injury after this age does not affect growth.

8.1 Current practice

Fractures of the distal tibial growth plate are estimated to account for 40% of growth plate injuries in children [3,6,11]. If undisplaced, treatment typically involves immobilisation in a plaster cast. If displaced, then the need for realignment is debated. Realignment typically involves surgery with general anaesthesia to restore the anatomy. This may involve simple manipulation, or may involve open surgery with fixation to hold the bone in position (i.e. metal screws or wires). Following surgery, patients are typically managed in a plaster cast.

Whilst surgery to realign the bone is often considered for displaced fractures, it is unclear if performing this surgery improves the outcome for patients. Proponents of surgery argue that restoring the anatomy realigns the growth plate and therefore maximises the opportunity for normal growth. Opponents argue that the procedure to realign the bone is itself a secondary injury to the growth plate, and that the procedure is unnecessary as the growth plate will remodel the deformity over time. The evidence within the literature is entirely equivocal as to whether realigning these injuries reduces the rate of growth disturbance.

8.2 Why is this important?

The most common type of growth plate injury in the distal tibia is a Salter Harris II fracture, accounting for over 50% of all injuries [6,10]. This injury represents trauma to the growth plate (physis), and a corresponding injury to the adjacent metaphysis. Prior studies have demonstrated that the mean age at the time of these injuries is 12.5 years, and almost all occur in children above 8 years old [5]. The complication of PPC following these injuries is reported to occur in 25% to 67% of cases [4,5,9,12–14]. PPC may result in clinical deformity, and the consequences may be lifelong, due to differences in the leg lengths or angular deformity, which may predispose an individual to pain and arthritis in the future.

As the second most common growth plate injury in children, these injuries represent a significant burden on health services. Given the ongoing debate, surgeons and families are keen to know whether surgery is superior to conservative treatment (no surgery).

Current evidence within the literature is contradictory and of poor methodological quality. The older literature related to these fractures suggested that complications were 'uncommon and rarely serious' [15], however more recent case series showed 40% of patients developed a PPC [4,5,8–12]. A systematic review of the low quality case series suggested no difference in PPC between surgery and conservative management of these fractures [6]. Given the uncertainty, some authors recommend surgery, whilst others recommend conservative treatment [5,10]. The ongoing uncertainty has prompted members of the British Society for Children's Orthopaedic Surgery (BSCOS) to prioritise this question as a top-5 trauma research priority [16].

9 OBJECTIVES AND OUTCOME MEASURES

Throughout this protocol the term 'parent' will be used in lieu of 'parent/guardian'.

9.1 Aim

The aim of the study is to evaluate the clinical and cost-effectiveness of surgical reduction, compared to conservative treatment, for the management of displaced Salter Harris II fractures of the distal tibial physis in children.

9.2 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 surgical correction have improved function compared with children treated with conservative care	Patient Reported Outcomes Measurement Information System (PROMIS) Mobility Score for Children	Baseline, 24 months post- randomisation	Completed PROMIS Mobility questionnaire	Patient-reported outcome measures that are submitted directly to the central CTU study team

9.3 Secondary objectives and outcome measures

To compare during the first 2-years post-randomisation between surgical reduction and conservative treatment:

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
Function	PROMIS-Mobility	Baseline, 6 weeks, 3, 6 and 12 months post-randomisation	Completed PROMIS Mobility questionnaire	Patient-reported outcome measure
Pain	Wong-Baker FACES Pain Score	Baseline, 6 weeks, 3, 6, 12 and 24 months post-randomisation	Completed Wong baker questionnaire	Patient-reported

				outcome measure
Quality of life	EQ-5D-Y	Baseline, 6 weeks, 3, 6, 12 and 24 months post-randomisation	Completed EQ-5D-Y questionnaire	Patient-reported outcome measure
Complication rate	Parent and site reported complications record	6 weeks, 8 weeks, 12 and 24 months	Completed Site Follow Up - Complications CRF and Additional Care CRF	Patient-reported outcome measure and CRF
Satisfaction with the cosmetic appearance of the leg.	VAS Cosmesis	3, 12 and 24 months post-randomisation	Completed VAS Cosmesis	Patient-reported outcome measure
Satisfaction with the treatment received	Satisfaction score	3, 12 and 24 months post-randomisation	Completed Satisfaction questionnaire	Patient-reported outcome measure
Educational participation	Bespoke 'Educational Participation'' questionnaire	6 weeks, 3 and 6 months post-randomisation	Completed days of 'Educational Participation' questionnaire	Patient-reported outcome measure
Leg Length	Leg length	12 and 24 months	Completed Leg length CRF	CRF
Angular deformity and PPC (growth arrest)	Angular Deformity, PPC	24 months	Completed Central Review CRF	CRF
Radiographs	Angular deformity	24 months	Radiograph	Medical notes
To estimate the cost-effectiveness of the treatments to the NHS and the broader economy, up to two years post-randomisation.	Bespoke Resource Use CRF	6 weeks, 3, 6, 12 and 24 months post-randomisation	Completed Resource Use CRF	Patient-reported outcome measure

Given the age of participants, patient reported outcomes will generally be self-reported by participants, with the exception of items relating to Satisfaction (with care), Resource use and Additional Care (complications), which will either be answered by the parent(s) or with the help of parent(s). A schedule outlining the timelines for data collection can be found in Tables 2 and 3.

Patient Reported Outcomes Measurement Information System (PROMIS) Mobility Score for Children (PROMIS-Mobility)

We will use the PROMIS-Mobility Computer-Adapted Test (CAT) (version 2.0). PROMIS-Mobility CAT is a validated tool to assess lower extremity function in children, which has been developed by the US National Institute for Health (NIH) for self-reported use in children from 8 years old [17,18]. PROMIS-CATs have been used successfully in other NIHR-HTA trials led by our group, including SCIENCE (17/18/02), FORCE (17/23/02) and CRAFFT (NIHR127674). Our research group have recently demonstrated the PROMIS mobility score in children correlates well with physical function measured using an accelerometer[19].

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. 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 outcome function. The 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. The PROMIS tools were developed in English, though two of the items in the PROMIS-Mobility tool are Americanised (i.e., the ability to walk 'a block' and I used a 'cane'). These will be Anglicised, with permission, to include a cultural translation (i.e., 'the length of a football pitch' and 'stick') in parentheses.

Wong-Baker FACES Pain Scale[20]

The Wong-Baker FACES pain score is a validated outcome 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. It is particularly useful amongst younger children, as only one third of children 5-14 years understand the concept of a Visual Analogue Scale (VAS).

EQ-5D-Y[21]

The EQ-5D-Y is the youth version of the EQ-5D-3L, which is a validated, generalised, health-related quality of life questionnaire consisting of 5 domains related to daily activities each with a 3-level response. EQ-5D-Y has been adapted for use amongst children, with both proxy and self-reported versions[21,22]. Given the age of participants within this study, as with the PROMIS tool, we plan to use the self-reported version throughout. There is currently ongoing work, to produce EQ-5D-Y value sets for use in children and adolescents. Our interim solution is to apply adult EQ-5D value sets to the EQ-5D-Y classification, but to use the EQ-5D-Y valuation system if ready before the ODD SOCKS study is complete. Utility valuations in the York A1 tariff set range from no problems on any of the five dimensions in the EQ-5D descriptive system (value = 1.0) to severe or extreme impairment on all five dimensions (value = -0.594).

Complications

All intervention complications will be recorded. The complications anticipated in the management of these patients are complications related to the cast (including, but not limited to, pressure areas) or complications related to surgery (including, but not limited to, wound infection, nerve injury, wound healing problems (overgranulation, hypertrophic/keloid scarring), malunion, non-union, re-fracture or broken metalwork). The need for further interventions or hospital admissions to treat any

complication will also be collected – i.e. revision surgery (i.e. to address bone infection or non-union), re-fracture and the later need to remove metal pins/screws (planned or unplanned).

Leg Length Measurement

This will be measured by a clinician experienced in limb length assessment and blinded to the treatment allocation. This will be performed using the 'Tape Measurement Method' measuring from anterior superior iliac spine to medial malleolus [23].

Angular deformity

Radiographic images for the purpose of study outcome assessment are to be at 24 months post-randomisation. This will include an Anteroposterior (AP) and Lateral (Lat) image of the affected ankle. We will also harvest images acquired as part of routine care, particularly those taken at diagnosis and post-intervention. The images at 24 months will be used to assess for any deformity (using the anterior distal tibial angle and the lateral distal tibial angle) and the presence or absence of PPC, recorded on the Central Review CRF. An independent adjudication committee will be formed to undertake radiographic measurements following a measurement protocol and, where possible, the treatment allocation will be concealed. Details of standardised protocols and proformas used by the adjudication committee will be outlined in the Data Management Plan (DMP).

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 will be collected.

Satisfaction (with care)

The perception of satisfaction with care will be collected using a 7 point Likert Scale (with 1 being Extremely satisfied and 7 being Extremely Unsatisfied).

Assessment of cosmesis (VAS)

The perception of cosmesis will be collected using a VAS (100 means the best appearance that you can imagine – like an ankle that has never been injured. 0 means the worst appearance you can imagine.)

Educational Participation

Parents will be asked to indicate the number of days their child did not participate in educational activities due to their injury and the resulting treatment.

9.4 Exploratory objectives/additional mechanistic objectives outcomes

There are no additional exploratory/mechanistic objectives/outcomes in this study.

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

PROMIS-Mobility CAT is the only validated tool to assess lower extremity function in children, which has been developed by the USNIH for self-reported use in children from 8 years old [17,18].

The follow-up schedule was decided by a group of clinicians and families, to ensure that it captured both short term outcomes, alongside longer-term problems that are associated with the growth of the child.

9.6 Use of core outcome sets (COS)

This study is informed by a core outcome set in lower limb injuries in children [24].

10 STUDY DESIGN AND SETTING

The ODD SOCKS study is a multi-centre, two-arm, superiority, randomised controlled clinical study.

The study will recruit 192 patients (96 in each of the 2 arms) with a displaced fracture of the distal tibia involving the physis and metaphysis (a Salter Harris II fracture) from approximately 30 planned sites in the UK. Participants will be randomised to receive Surgical Reduction or Conservative Treatment.

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

10.1 Summary of research

The project is a two-phase trial. Phase 1 (internal pilot) will confirm the expected rate of recruitment and pilot data collection procedures in a large-scale multi-centre randomised controlled trial. Phase 2 is the expansion of the pilot into the full definitive trial. Peer-reviewed publications of the main results will be generated after the completion of this phase.

10.1.1 Internal Pilot

The pilot will take place at a minimum of 20 centres over 9 months. The aims of the pilot phase are to determine the number of eligible patients recruited to each centre and assess the rate at which recruitment progresses and to optimise the procedures for recruitment. Electronic screening logs will be used by each site to determine the number of patients assessed for eligibility. The number of eligible and recruited patients, as well as those patients who decline to consent or withdraw, will be recorded and analysed.

10.1.2 Trial Structure

Children aged 8-15 years inclusive presenting to the trial centres with a displaced fracture of the distal tibia involving the physis and metaphysis (i.e. Salter Harris II) are potentially eligible to take part. Upon presentation, children will receive analgesia and their ankle will be assessed to ensure that the fracture does not require an emergency realignment (i.e. compromising the blood or nerve supply to the foot, or causing potential damage to the skin and other soft tissue structures). Once any emergency realignment is either performed, or confirmed to not be required, temporary immobilisation of the limb for comfort will be applied as per the usual practice of the treating centre. In many hospitals the decision related to definitive treatment is taken in the emergency department by the on-call orthopaedic surgical teams; in others the child may be discharged to an early appointment in the fracture clinic. Owing to the nature of the condition and treatment pathways, the study will be introduced to the patient at the point where definitive care is planned.

After informed consent/assent has been obtained, baseline demographic and injury data, physical function using the PROMIS Mobility CAT, pain-intensity using the Wong-Baker FACES Pain Scale and health-related quality of life using the EQ-5D-Y will be collected.

Randomisation will be 1:1 to either surgical reduction or conservative treatment, by minimisation using a computer-based randomisation system. The minimisation algorithm will stratify by biological sex, participant age group (8-12 years, 13-15 years)and whether any emergency realignment was performed.

During follow-up, participants will be asked to complete further questionnaires on function, pain, quality of life, satisfaction (with care and cosmesis), additional surgery and complications (Additional Care CRF), educational participation, and health resource use. Radiographs of the ankle will be taken at 24 months post-randomisation. All participants will be followed-up for two years.

Patient reported outcomes will be collected electronically (with a telephone interview where required) with email and/or text message prompts.

10.2 Recruiting sites/site types

Patients will be screened from the emergency department and/or fracture clinics at the recruitment centres. All patients meeting the inclusion criteria will be screened and assessed for eligibility. Electronic screening logs will be kept for each recruitment centre to determine the number of patients assessed for eligibility and reasons for any exclusion. The screening logs will contain non-identifiable information such as the child's age and injury severity, which will allow for an assessment of the generalisability of the study.

Refer to section 26 for information on identification and management of sites.

10.3 Collection of outcome data and follow-up assessments

Baseline clinical and complication data will be completed during the primary and routine follow-up clinical appointment (8 weeks) by the recruiting team. For participant data, an advance notification will be sent when questionnaires are due and then the parent and/or child will be prompted to complete questionnaires at 6 weeks, 3 months, 6 months, 12 months, and 24 months. Questionnaires will generally be self-reported, however parent input will be advised when completing the satisfaction with care, health-economic (Resource Use) and complication (Additional Care) questionnaires. A direct link to the on-line questionnaire will be sent via a text message or email. If the participant and/or their parent have not responded to the initial and reminder messages within a specified timeframe (the time allowed will vary for each of the time points as per DMP, or if the central CTU study team have queries relating to data that has been entered by the parent and it is not appropriate for the site to answer these, we will attempt to contact the parent to obtain (or request clarification of) the outcome data for the time point over the telephone or by email/text. This contact will come from the central CTU study team at the University of Oxford. Exact timelines and frequency of phone calls will be specified in the DMP for this study.

If the parent indicates that a complication or an additional surgery has occurred, the database will be checked to ensure that a complication form has been completed, and, if not completed, sites will be prompted to complete this form to give full details of the event.

Refer to section 17.3 for full details of outcome data collection and follow-up assessments.

10.4 Countries of recruitment

UK.

10.5 Duration of participant involvement

Participants will be in the study for approximately 24 months from randomisation to last protocol visit.

10.6 Post-study treatment/care and follow-up

Following a participant's final protocol visit, they will receive standard care.

10.7 Central review procedures

Angular deformity and Growth Arrest will be recorded on the Central Review CRF. Refer to section 9.3- Angular Deformity.

10.8 Use of Registry/NHS Digital data

Pending future funding, ethical approval and patient consent, we will look to collect long term outcomes using data linkage with national datasets and clinical registries. In order to consent participants who have agreed to be contacted to long term follow up in the future, we will collect and

store participants' contact details and their NHS/CHI/H&C number for a period of five years after the study has ended, or 12 months after the youngest participant turns 16, whichever is longest. Consent for the storage of these details will be collected from parents initially, with further consent from participants upon reaching the age of 16 years.

10.9 Expected recruitment rate

We recognise that unlike amongst adult fractures, there is a very large seasonal variation in fractures in children. Approximately 4-5 times more fractures are seen in mid-summer compared to mid-winter, with weather significantly influencing the incidence of fractures – correlating with time spent playing outside [25]. The expected recruitment rate will be adapted to accommodate this large seasonal variation. We anticipate achieving an average conservative rate of between 0.4 and 0.5 participants per centre per month.

It is likely that 3 summer periods will be required in our total recruitment period. Our experience in conducting research in children's orthopaedics shows us that in trials randomising between surgery and conservative treatment, consent rates (i.e. the conversion from screened to recruited) have been around 60% (NIHR HTA SCIENCE Study & CRAFFT Study). We have planned for a conservative consent rate of 50%.

10.10 Equality, diversity and inclusion for study participants

The NIHR INCLUDE guidance has been carefully reviewed and considered during the planning of the ODD SOCKS trial. Young people under the age of 18 have been identified as an under-served group and ODD SOCKS will therefore help by directly targeting this group. We have spent time identifying potential barriers and challenges faced by our study population and used these to shape our recruitment strategies and engagement approaches. We will ensure that our trial respects the rights and welfare of participants from underrepresented backgrounds within our study population, for example by providing help and assistance to those families and patients who are digitally or educationally disadvantaged. We will actively collect demographic data to track the representation of underrepresented populations. The NIHR INCLUDE guidance has been instrumental in ensuring that our research trial is conducted in a sensitive, inclusive, and meaningful manner, ultimately contributing to addressing the historical disparities in clinical research participation.

Recruitment will occur in a range of emergency settings (emergency department and orthopaedic fracture clinics), to ensure that the study is broadly representative of the patient population. Recruitment materials have been optimised, with families, to ensure that they are broadly appealing, and are able to communicate effectively with families from a range of educational backgrounds. Recruitment will occur across the UK, to ensure that the result is broadly generalisable.

10.11 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 ODD SOCKS study will recruit children aged 8-15 years old inclusive, with a displaced fracture of the distal tibia involving the physis and metaphysis (Salter Harris II (SHII)).

Written informed consent must be obtained before any study specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the PI based on the below criteria.

11.3 Inclusion Criteria

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

- They are aged 8 to 15 years old inclusive.
- There is radiographic evidence of a displaced fracture of the distal tibia involving the physis and metaphysis (SHII); with or without a corresponding fibula fracture.
- The treating clinician believes that they may benefit from surgical reduction +/- fixation.

11.4 Exclusion Criteria

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

- The injury is more than 7 days old.
- The fracture is open.
- They have an intra-articular fracture that requires fixation to restore the joint surface.
- They have any other contralateral (opposite-sided) ankle fracture/injury.
- There is evidence that the patient and/or parent/guardian would be unable to adhere to trial procedures or complete follow-up.
- The patient has previously been enrolled into the ODD SOCKS Study.

11.5 Rationale for inclusion and exclusion criteria

The inclusion criteria represent the patient group for whom there is clinical uncertainty in treatment. Injuries more than 7-days old may be complicated to treat for several reasons and therefore may not be representative of typical SHII distal tibial fractures. Open fractures and intra-articular fractures requiring restoration of the joint surface are specific indications for surgical treatment and therefore a position of equipoise does not exist. Contralateral ankle fractures/injuries would lead to a situation where the outcome cannot be accurately attributed to the SHII distal tibial fracture and therefore are excluded. Whilst we have sought to maximise inclusion, if there is evidence that the patient or family would be unable to adhere to trial procedures or complete follow-up, their involvement would be inappropriate.

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, PIs should contact the central CTU study team, who will contact the CI or designated clinicians as necessary. If in any doubt the CI 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 the central CTU study team for clarification if any instructions seem ambiguous, contradictory, or impractical. Clinical queries must also be directed to the central CTU study team. All clinical queries and clarification requests will be logged, assessed and a written response provided. 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 27.7.

12 SCREENING AND RECRUITMENT

12.1 Participant Identification

Patients will be identified in the accident and emergency departments, fracture clinic or hospital ward of participating hospitals. Relevant clinical staff will be made aware of the study being conducted at their institution. They will flag any potentially eligible patients and briefly introduce the idea of the study to the patients and their parents. With permission, a researcher will then approach the patient/parent for the informed consent and assent discussions. Identification of potential participants will be done by the direct care team. They will alert the researcher who will perform initial eligibility checks on the patient and inform the treating clinician that the patient is a potential participant.

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

- Searching of clinic records/hospital databases by the usual care team to identify individuals that may be eligible to enter the study
- Identification during fracture clinic visits

12.1.1 Identification of participants via clinic records/hospital database

Potentially eligible patients will be identified by searching of clinic records/hospital databases at participating research sites by those in the clinical care team only. Any patients who are thought to fulfil the inclusion/exclusion criteria will be contacted by the clinical care team and informed of the study.

12.1.2 Identification of participants during fracture clinic visits

Potentially eligible patients identified during fracture clinic visits will be shown a Patient Information Sheet (PIS) 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 who 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 visits. When a potential participant is 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.

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

Not applicable for this study. Re-screening of ineligible patients is not permitted.

12.3 Use of screening logs

A screening log (within the Research Electronic Data Capture (REDCap) study database) will be used to record information about the number of patients considered and/or approached for the study and if provided, the reasons for declining participation. Personal identifiable data will not be recorded on the screening log; a screening number will be assigned to each patient screened.

13 STUDY INTERVENTION AND COMPARATOR

All of the hospitals involved in this study are familiar with both study treatment techniques. All patients will initially receive temporary immobilisation and analgesia at the discretion of the treating clinician, as per any local or national guidelines (i.e. Royal College of Emergency Medicine best practice guidelines for the management of acute pain in children).[26] Randomisation will occur at the point where the treating clinician believes that the child would benefit from surgical reduction with or without fixation.

13.1 Surgical Reduction (intervention)

Surgical reduction with or without fixation will be performed. The bones will be realigned under general anaesthesia or sedation altering the conscious state of the child. It may be possible to achieve realignment without making a skin incision, or an incision may be required. The need for an incision, type and position of incision and method used to hold the bones in position will be at the discretion of the clinician; i.e. plaster cast alone, plaster cast and screws/wires, plaster cast and plate and screws. A record will be made of the operative details, the cast details and any cast changes. Following surgery, usual practice is for the leg to be immobilised in cast for 4-6 weeks. Specific details on the techniques and materials used in theatre will be collected for each participant.

13.2 Conservative Treatment (usual care/comparator/control)

This technique involves the application of a plaster cast to hold the bone fragments in the optimal position without giving medication to deliberately alter the conscious level of the child. This may be the initial plaster cast used to stabilise the fracture, or the plaster cast may be changed by the clinician to maximise patient comfort and fracture stability. Although the principles of applying a plaster cast are inherent in the technique, in this pragmatic trial the type of casting material, extent of the cast and the details of the technique will be left to the discretion of the treating clinician as per their usual practice. A record will be made of the cast details and any changes. Usual practice is for the plaster cast to be used for 4-6 weeks.

14 INFORMED CONSENT

14.1 Consent Procedure

A member of the clinical team will initially approach the patient and their parent(s), either face to face or in a virtual remote clinic. If the family is interested in potentially participating, they will be introduced to a local research associate, and presented with a study 'explainer video', a public website containing all relevant information, and a verbal explanation of the study procedures. Age-appropriate

information sheets are also available to be downloaded and/or printed from the public website – though our parent and child advisors are keen that these are only printed when necessary. We have performed a study within a trial (within the FORCE Study), which demonstrated that families preferred online materials, compared to traditional consent material, and that they increase trial recruitment rates. Parent co-applicants and members of the Parents Advisory Group (PAG) have identified the key information that they wish to have simplified for them in a trial animation, and materials are presented in a readily digestible format.

After the information is delivered, the family will be given the opportunity to discuss issues related to the study with the research team, the treating clinician, and family and friends. The individual seeking consent will ensure that the child and parent have fully understood the information provided and are willing to consent / assent.

14.2 Time allowed to decide to take part

Clinical care teams will try to ensure study materials are shared with patients as soon as possible following the diagnosis to enable them to have the maximum opportunity to consider the study.

14.3 Completion of the Informed Consent Form

The parent and the PI (or authorised designee) must personally sign and date the current approved version of the informed consent form.

The parent will be asked to sign an electronic informed consent form (with the consent form being filled in directly on the study database, REDCap). All children will also be asked to provide their assent to take part by signing an electronic assent form. A copy of all electronic consent and assent forms will be emailed to the parent directly. Where it is not possible for a consent form to be completed in clinic, remote electronic consent may also be used. Where consent forms are completed electronically, signatures will be either achieved by a finger tracing across a tablet device, or 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.

A copy of the electronic consent form downloaded from the study database should be placed in the ISF and in the participant's medical record.

Parents will be required to give consent for all aspects of study participation for their child to take part in the study.

14.4 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.

14.5 General Practitioner (GP) notification

Fractures are almost exclusively managed in secondary care, primarily under the care of orthopaedic surgeons. We have discussed children's fracture care with a range of GPs, and whilst they were interested to know about the occurrence of the injury, they felt that detailed intricacies related to the fracture pathways and treatment modalities were unnecessary. GPs wished to receive the current standard clinical documentation (i.e. a dictated outpatient letter), that may include

reference to the study, though they felt specific study information beyond this was overly burdensome to their workload.

14.6 Re-consenting

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

Participants who turn 16 years of age prior to the collection of the final 2-year post-randomisation outcome time point will be asked to consent to continuation of participation. Consent will be requested prior to the next planned follow-up time-point for the participant. Participants who decline to consent will be withdrawn.

Consent will also be sought via an email from all participants who turn 16 years of age after they have completed the study, in order to store personal data, allowing the central CTU study team to contact them in the future for the purpose of long-term follow-up.

Any new information that arises during the study that may affect parents' or participants' willingness to take part will be reviewed by the Trial Steering Committee (TSC); if necessary, this will be communicated to all parents and participants by the Trial Manager. A revised consent form will be completed if necessary.

14.7 Participants who lose capacity during the study

In the unlikely event that the participant loses capacity to consent during the study, the participant would be withdrawn from the study. Identifiable 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.

15 RANDOMISATION

15.1 Timing of randomisation

The patient will be randomised after consent and baseline data have been obtained, either in the emergency department, or in a fracture clinic (face-to-face or virtual clinic- if virtual, site will inform the parent/guardian of the treatment allocation). All hospital treatment areas have access to the internet so will access the randomisation service in real time, i.e. there will be no delay to patient treatment.

15.2 Randomisation procedure

Randomisation should take place once informed consent has been given. Eligibility will be reconfirmed at randomisation. Participants will be randomised by the site research team via the ODD SOCKS REDCap study database.

Participants will be randomised to one of the following treatment arms:

Arm	Treatment
Surgical Reduction (intervention)	Surgical Reduction with or without fixation. The bones will be realigned under general anaesthesia or sedation altering the conscious state of the child.
Conservative Treatment (usual care/comparator/control arm)	Application of a plaster cast to hold the bone fragments in the optimal position without giving medication to deliberately alter the conscious level of the child.

Upon randomisation of a participant the central CTU study 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 TMF.

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 (ref GitHub - Nottingham-CTU/REDCap-Minimization: REDCap External Module: Perform minimization.)Allocation will be minimised to ensure balance for:

- biological sex
- participant age group (8-12 years, 13-15 years)
- emergency realignment performed

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 randomisation schedule will be designed by the OCTRU trial statistician and full details will be detailed in the randomisation and blinding plan.

15.3.1 Justification for stratification factors

Stratification by biological sex will ensure balance because males have better remodelling capacity than females of the same age during childhood, owing to different rates of skeletal maturation.

Stratification by participant age will ensure balance, because although younger children have better remodelling capacity than older children, they also have more growth remaining and therefore more time for deformity to develop if the growth plate is damaged.

Stratification considering whether emergency realignment was performed will ensure that magnitude of initial deformity is captured. In some instances, the fracture needs emergency realignment to avoid damage to skin, blood vessels or soft tissues. Once all emergency procedures are completed, the fracture position may be assessed against the criteria for inclusion.

15.4 Back-up randomisation procedure

There is no back-up randomisation procedure for this study.

16 SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

There are currently no planned sub-studies, translational studies, or 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

Participants and/or their parents will be asked to complete a set of baseline questionnaires after providing consent, but prior to being allocated one of the two study treatments. Table 2 shows participant data collection time points.

After the allocated treatment has been provided, the research team will complete a treatment form. Follow-up clinical data (i.e., routine records check related to planned and unplanned care) will be collected at 8 weeks, 12 months, and 24 months post-randomisation (see Table 3).

17.2 Study questionnaires

Questionnaires will generally be self-reported, however parent input will be advised when completing the satisfaction with care, resource use and complication questionnaires. Questionnaires will be sent via email/text to parents, and children over 12 if they agreed to be contacted. Refer to section 10.3.

17.3 Data Collection

Baseline clinical and complication data will be completed during the primary and routine follow-up clinical appointment (8 weeks) by the recruiting team. For participant data, an advance notification will be sent when questionnaires are due and then the parent and/or child will be prompted to complete questionnaires at 6 weeks, 3 months, 6 months, 12 months, and 24 months.

17.3.1 Baseline

Table 1 Baseline Data Collection

Data sourced/collected by site research team	**Data directly reported by participants (patient-reported outcomes)**
Trial intervention (Treatment CRF)	PROMIS Mobility (Primary Outcome)
	EQ-5D-Y
	Wong Baker FACES Pain Score

17.3.2 Follow-up assessments/subsequent visits

Follow-up questionnaires will be sent to parents at 6 weeks, 3 months, 6 months, 12 months and 24 months. Details of Participant CRFs collected at each time point are described in Table 2 below.

Table 2 Participant Data Collection time points

Procedures	Screening	Baseline	6 weeks	3 months	6 months	12 months	24 months
Informed Consent +/- Assent	x						
Demographic Data	x						
PROMIS Mobility (Primary Outcome at 24 months)		x	x	x	x	x	**x**
EQ-5D-Y / Wong Baker FACES Pain Score		x	x	x	x	x	x
Resource use			x	x	x	x	x
Educational Participation			x	x	x		
VAS Cosmesis/ Satisfaction with care				x		x	x
Additional Care CRF (Complications)			x			x	x

Participants will usually attend orthopaedic follow-ups as part of standard care until at least 2 years after the initial assessment, to monitor for signs of growth disturbance. During these visits, the clinical team will perform a clinical assessment and a radiographic examination will normally occur. At all clinic visits, the research team will record any complications that have occurred.

Table 3 Site Data Collection time points

Procedures	Screening (clinic/virtual clinic)	Baseline (clinic/virtual clinic)	8 weeks clinic	12 month clinic	24 month clinic
Assessment of Eligibility Criteria (Screening log)	x				
Informed Consent +/- Assent	x				
Trial intervention (Treatment CRF)		x			
Week 8 Follow Up Immobilisation CRF			x		
Site Follow Up Complications CRF			x	x	x
Study Measurements: Leg Length Discrepancy				x	x
Radiographs					x

17.4 Communication with study participants by the central CTU study team

Participants will be notified to complete study questionnaires by e-mail and/or text message if they are over 12 years old and agreed to be contacted, otherwise questionnaires will be sent to the parent. Parents/participants may be sent reminder messages and 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 questionnaire. Parents/participants will receive an initial e-mail/and or text message and reminder messages by a member of the central CTU 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 and 24 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'.

Participants may also be withdrawn from the study (or aspects of the study) by their clinician if they believe the participant needs to be withdrawn.

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

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

Participants (or their parents) may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the participant receives. Participants (or their parents) can withdraw by contacting the research team, using the contact details found on patient information materials and the trial website. Participants (or their parents) will **not** have the option to withdraw the data collected up until the point of withdrawal, as the data will be required for the intention-to-treat (ITT) and safety analysis. The options for withdrawal will be explained clearly in the PIS. The type of withdrawal and reason for withdrawal, if the participant is willing to provide one, will be recorded in the withdrawal CRF. Contact details for these participants will be destroyed. Withdrawn participants or participants deemed ineligible after randomisation will not be replaced.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the Central CTU study team. Appropriate action will be taken by the study teams (centrally at the CTU 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 relevant communications which the participant had consented to receive regarding their participation are no longer sent.

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. The outcome data will be collected directly from the patient and their parents.

The CI, Trial Management Group (TMG) and Trial Statistician will not be blinded.

Outcome assessors will be blinded to the participant's treatment allocation. For outcomes that could potentially be affected by bias (i.e. primarily radiographic measurements), an independent panel of experienced orthopaedic surgeons, blinded to the intervention where feasible (i.e. no metalwork), will review and interpret the radiographs.

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 SAFETY REPORTING

20.1 Safety reporting period

Safety reporting for each participant will begin from the first point of administration of the intervention and will end when the participant has reached their final main follow up time point, at 24 months post-randomisation. This is a low risk, pragmatic trial where both trial interventions are in

common use. Considering this, we do not anticipate many serious adverse events (SAEs) associated with either treatment.

20.2 Definitions

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	An SAE 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] If a 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.

20.3 Expected adverse events

For this trial, foreseeable adverse events include the following (including the need for hospital admission and/or further unplanned surgery to manage these complications in either group):

(a) Complications related to the cast (including, but not limited to, pressure areas) or
(b) Complications related to surgery (including, but not limited to: wound infection, nerve injury, wound healing problems (overgranulation, hypertrophic/keloid scarring), malunion, non-union, re-fracture or broken metalwork).

Planned surgery for the removal of metal pins/screws/ plates will be recorded as part of routine treatment and will not be regarded as a complication.

20.4 Reportable Aes/SAEs

Aes that are foreseeable in the treatment of these fractures do not need to be reported immediately, provided they are recorded in the Additional Care/Site Follow up Complication CRFs.

For the purpose of safety recording for this trial, only unexpected SAEs potentially related to the intervention will be reported to the central CTU study team.

20.5 Non-reportable Aes/SAEs

Aes that are unrelated to the injury, intervention or treatment 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 20.3 (such as tingling, pins and needles/discomfort, sensation of warmth/cold), will also not be reported.

20.6 Procedure for collecting safety events from sites/participants

These events will be recorded on patient-reported questionnaire (Additional Care) and by the site in the Site Follow Up Complications CRF if they become aware of such an event.

20.7 Reporting of SAEs from sites to the central CTU study team

Only SAEs considered by the PI to be related (possibly, probably, or definitely) to the study intervention/any of the research procedures will be reported immediately to the central CTU study team. Such events will be reported immediately to the central CTU 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 should be used as a back-up if the SAE form is not available electronically. This should be e-mailed to the central CTU study team within 24 hours of becoming aware of the event. The central CTU study team will acknowledge receipt of any SAEs reported via e-mail within one working day and provide the site with a unique SAE Log number.

Refer to section 20.5 for events that do not require reporting.

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

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

20.8.1 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:

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

20.9 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.

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

All intervention/study procedure **related** SAEs will be recorded and reported to the REC as part of the annual reports. 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. All such events will also be reported to the TMG, TSC and the Data Safety and Monitoring Committee (DSMC) at their next meetings.

20.11 Unblinding of SAEs for reporting to the REC

Not applicable. There is no blinding in this study.

20.12 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 CTU study team. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

21 PREGNANCY

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

22 STATISTICAL CONSIDERATIONS

22.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a separate SAP that will be drafted before the study opens and finalised prior to the final analysis data lock. The SAP will be written by the Study Statistician in accordance with the current OCTRU SOPs and will be finalised and agreed by the trial statistician, the CI and the TMG. The DSMC will review and, if necessary, provide input into the SAP.

22.2 Sample Size/Power calculations

172 participants providing data on the PROMIS Mobility Score for children at 24 months post-randomisation (86 in each group) will have 90% power to detect a difference in means of 5 assuming the SD is 10 using a two-group t-test with a 5% two-sided significance level. This is inflated to 192 patients (96 per arm) allowing for 10% attrition.

Raw scores of the PROMIS Mobility Score for Children are translated into standardised T-scores with a population mean of 50 and an SD of 10. The minimal clinically important difference (MCID) of PROMIS paediatric measures is generally 3.0-5.0 [27,28].

We discussed with young people and families our experience from previous trials, in particular that families are reluctant to be randomised to surgery unless there is a marked improvement to be gained. Parents were extremely anxious about surgery, and we have learned their strong sense of responsibility when ‘subjecting their child to surgery’, believing the benefit must significantly outweigh the perceived risks. We therefore seek an effect size at the upper range of the MCID. Other studies have similarly highlighted that patients often seek greater effect sizes to warrant surgical interventions than the established MCID.[29]

22.3 Description of Statistical Methods

Results will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement and any appropriate extensions and will be described fully in a separate SAP. A single final unblinded statistical analysis will take place after all follow-up has been completed, and sufficient time has been allowed for data collection and cleaning.

Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and standard deviations (SD) or medians and interquartile ranges as appropriate for continuous variables and numbers and percentages for binary and categorical variables.

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

22.3.1 Primary outcome

The PROMIS Mobility Score for Children at 24 months is the primary outcome of the study and the primary analysis will compare the treatment groups in a linear mixed effects model including all patients, all time-points and adjusting for the stratification factors as fixed effects, with centre as a random effect. A treatment by time interaction will be included, and the model is anticipated to use an unstructured covariance matrix and restricted maximum likelihood. The analysis will adjust for the stratification factors (recommend by ICH–E9) – this will have a greater power to detect the minimum important difference than the unpaired t-test which was used for the power calculation [30]. A secondary analysis will compare treatment groups using analysis of covariance adjusted for baseline scores to explore consistency between the treatment effect. The adjusted mean difference between groups will be presented, together with 95% CI and p-values.

22.3.2 Secondary outcome(s)

Continuous secondary outcomes will be analysed using a mixed effects model as per the primary outcome, with model adjustment for baseline scores/values and stratification factors. These will be reported as an adjusted mean difference with 95% CIs and p-values. Binary outcomes will be reported in terms of relative and absolute risk, analysed using logistic regression adjusted for stratification factors.

The number of complications will be presented by treatment arm, and the proportion of participants who receive at least one complication will be analysed as a binary outcome.

22.4 Inclusion in analysis

The principal analysis will be performed on the as randomised (ITT) population, analysing participants with available outcome data in their randomised groups, regardless of adherence or actual treatment received. The study will be reported in line with CONSORT guidelines.

22.5 Subgroup analysis

We will explore consistency of the primary treatment effect for important diagnostic subgroups. We will confirm the final subgroups in the SAP, but as a minimum, these will include the stratification factors sex, age (8-12 years and 13-15 years) and whether any emergency realignment was performed.

22.6 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.

22.6.1 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.

22.7 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.

22.8 Procedure for accounting for 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. The sample size calculation incorporated an inflation to account for potential loss to follow-up. The main analysis of the primary outcome will use a mixed model which will include all participants who have at least one set of outcome data.

22.9 Procedures for reporting any deviation(s) from the original statistical analysis plan

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

22.10 Internal pilot/Decision Points

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 determine the number of eligible patients recruited to each centre and assess the rate at which recruitment progresses and to optimise the procedures for recruitment.

Stop-go criteria decisions will be determined with the oversight committee and funder after 9 months of recruitment.

The TMG will closely monitor the progression criteria during the internal pilot, and together with the TSC and DSMC will perform a full review towards the end of the internal pilot. The TSC and funder would make the final decision to terminate the study.

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, participants will be followed up as per protocol.

23 HEALTH ECONOMICS

We have integrated an economic evaluation, informed by the NICE Reference Case[31] and reported according to the Consolidated Health Economic Evaluation Reporting Standards statement [32]. The economic evaluation will be conducted from the perspective of the UK NHS and Personal Social Services. A Health Economics Analysis Plan, providing full details of the prospective economic analysis, will be finalised before the end of follow-up.

Participant's use of primary, secondary and community care services, as well as medications will be collected using an electronic resource use questionnaire [33]. The resource use questionnaire will be designed with 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 status will be determined using the EQ-5D-Y questionnaire, with utilities derived based on the UK adult tariff, or an age-specific valuation set if this becomes available. Quality-adjusted life-years (QALYs) will then 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 [34,35]. The primary economic outcome will be the incremental cost-effectiveness ratio 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. Economic outcomes from the trial will be used to parameterise a decision analytic model, which will be used to assess future costs and benefits. Parameters which cannot be derived from within the trial will be sought from the wider literature. Uncertainties in parameter inputs will be accounted for with parametric distributions for each point estimate. This will enable probabilistic sensitivity analyses to be performed using Monte Carlo simulation.

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

24 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the study-specific DMP. See section 28 for information on management of personal data.

24.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. Source data is outlined in section 9.

24.2 Location of source data

The location of source data in the study is listed in the tables within section 9.

24.3 Case report forms (CRFs)

The PI 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 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 and contact details form, the participant will be referred to by the study participant number/code, 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).

24.4 Non-CRF data

Imaging data will be collected to determine angular deformity- these will be held on an application called TRIAGE- further information will be described in the study specific DMP.

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

24.6 Data Recording and Record Keeping

The CRFs will be designed by members of the study management team which will include the CI, study statistician(s) and TM.

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.

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 will be entered into the study database by suitably trained central CTU study staff. Full details of this process will be recorded in the DMP. 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).

Refer to section 28.4 for details about retention of participant identifiable data.

24.7 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 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.

25.1 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.

25.2 Study monitoring

Monitoring will be performed by the central CTU 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. 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 CTU 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 PI 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.

25.3 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 CTU study team without delay.

25.4 Study committees

25.4.1 Trial Management Group (TMG)

A 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.

25.4.2 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.

25.4.3 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.

26 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

26.1 Identification of recruitment sites

Recruitment sites will be selected based on 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 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.

26.2 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 a delegation log provided by the central CTU 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 the delegated responsibilities.

26.3 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 CTU 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 CTU study team. The Central CTU 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 REDcap data collection system and are able to begin recruiting participants.

26.4 Training

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

26.5 Study documentation

The central CTU study team will provide an electronic ISF to each participating site containing the documents needed to conduct the study. The central CTU 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 ISFs as necessary to reconstruct the conduct of the study.

27 ETHICAL AND REGULATORY CONSIDERATIONS

27.1 Declaration of Helsinki

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

27.2 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.

27.3 Ethical conduct of the study and ethical approvals

The protocol, PIS, informed consent form 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.

27.4 NHS Research Governance

Once HRA & HCRW approval is in place for the study, sites will confirm capability and capacity to participate in the study.

27.5 Protocol amendments

All amendments will be generated and managed according to the OCTRU SOPs to ensure compliance with applicable regulation 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 (in nature or severity) 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.

27.6 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 CTU study team. Examples of important deviations are those that might impact on patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see section 27.9).

27.7 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 PI must inform the central CTU 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 CTU 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 CTU study team will follow written procedures to implement the changes accordingly.

27.8 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **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 CTU 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.

27.9 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.

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

27.10 Study Reports

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

27.11 Transparency in Research

Prior to the recruitment of the first participant, the study will be registered on a publicly accessible database (ISRCTN16320803), 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 33

27.12 Use of social media

Social media (e.g. X (formerly 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 ay a site etc).

28 PARTICIPANT CONFIDENTIALITY

28.1 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 e-mail
- 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 PIS explains what contact details will be collected and how these will be used.

Site staff at participating sites will ensure that contact details for study participants are up to date when participants attend for study visits.

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

28.2 Storage and use of personal data

Personal data during the study 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 such a way that is satisfies the requirements of the UK General Data Protection Regulation (GDPR) and requires data to be anonymised as soon as it is practical to do so.

All electronic patient-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 Investigator site 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.

28.3 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 CTU 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 participant's direct healthcare team will not have access to personal identifiable data until the participant 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 participant's medical notes.

The PIS clearly describes who will have access to the participants personal identifiable data during the study and explicit consent is obtained from study participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the University of Oxford, Alder Hey Children's NHS Foundation Trust, 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.

28.4 Destruction of personal identifiable data

Personal identifiable data will be kept 5 years after the study has finished or 12 months after the youngest participant turns 16, whichever is longest, for those who consent to be contacted for a potential long term follow up. For those who do not agree to be contacted for a long term follow up, personal identifiable data will be kept for 12 months after completion of the study.

28.5 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.

29 PUBLIC AND PATIENT INVOLVEMENT (PPI)

29.1 PPI in study design and protocol development

Families affected by this injury, and a PAG, have been very important in the design of the study - including working out what the most important outcome is for the study. Children and young people have keenly contributed to making the trial 'animation', which has been 'tested' out in schools and amongst families care for similar injuries to ensure that they can tell the trial 'story' in a fair way.

Patient information materials have been written to broadly appeal to children and parents. We have discussed this content in detail with the NIHR Young Persons Advisory Group (YPAG) - who principally

range in age between 11 and 16 years old), PAG, health care professional and our PPI advisors. The online content is an extensive package of multimedia content which children and parents agreed was readily accessible to all. Online content is readily available in all locations, and is optimised for different device viewing (i.e. mobile vs. desktop). We previously conducted a study within a trial (SWAT) embedded in another large children's trauma trial (FORCE), evaluating our online multimedia content vs. conventional patient materials[36] . The online materials were found to be easier for participants to understand and were more likely to be evaluated positively.

Families are keen to be involved in the ongoing running and oversight of this study.

29.2 PPI during the study

A PPI representative will be an integral member of the TMG.

29.3 Dissemination of study results

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

30 EXPENSES/PAYMENTS TO PARTICIPANTS

Recompense for data costs caused considerable debate amongst our PPI forum (through the NIHR YPAG and PAG). It was recognised that cost may be a barrier to participation for some families (i.e. particularly those from more deprived groups, who frequently use pay-as-you-go data tariffs); whilst others believed that automatically offering recompense for participation would be a barrier to them – as they believed the NHS could ill-afford to make such payments. Agreement was therefore made to offer a payment of £10 to cover reasonable out of pocket expenses, rather than for this to be automatically provided. We have incorporated this approach in our study by offering a £10 gift e-voucher at the end of the 24-month questionnaire, as a 'thank you' and to compensate for costs incurred through completing the questionnaires (i.e. mobile phone data).

31 SPONSORSHIP, FINANCE AND INSURANCE

31.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship. A separate study-specific delegation of responsibilities will outline the responsibilities of the CI, Sponsor and OCTRU.

31.2 Funding and support in kind

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

Funder(s)	Financial and non-financial support given
National Institute for Health and Care Research (NIHR) Health Technology Assessment	NIHR132675

31.3 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.

32 CONTRACTUAL ARRANGEMENTS

Alder Hey Children's NHS Foundation Trust acts as the contractor for this project for the NIHR. 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.

33 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/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the CONSORT including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

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

The health economics analysis plan will be published in an open-access journal before recruitment is completed.

33.1 Study results

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

33.2 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 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. No patient identifiable information will be contained in any form of dissemination of study results.

Dissemination of results will include the following methods:

Multimedia: A study dissemination website will be produced, which lay summaries the study results alongside a study dissemination video, clinical pathways, multi-language modifiable patient information leaflets and links to the journal articles (see www.FORCEstudy.org for example).

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 (emergency medicine doctors, orthopaedic surgeons, emergency nurse practitioners and trainees in emergency medicine and orthopaedics). It is expected that findings from this study will be presented at national and international conferences.

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. Given the frequency of the injury, this is also likely to be of interest to international press-outlets.

Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (e.g. Twitter and online fora such as MumsNet), with the explainer video and infographic. We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal'.

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 Oxford and Alder Hey Hospitals NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR partners, we will agree upon effective communication strategies including co-ordinated press releases, interviews etc. Finally, we will produce an initial Wikipedia page for this injury (currently absent) and include details of the study result.

It is possible that the results of the study may influence national guidelines, particularly in the form of the British Orthopaedic Association Standards for Trauma (BOAST) guidelines. As a result, we will ensure that stakeholders from the BSCOS and the British Orthopaedic Association (BOA) are notified formally of the results in order to inform development of such guidelines.

33.3 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, OTEC and the Sponsor.

34 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.

35 ARCHIVING

35.1 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, whichever is longer.

35.2 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.

35.2.1 CTU Trial Master File

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

35.2.2 Investigator Site File and participant medical records

The ISFs 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.

35.3 Retention of data sets

After the end of the study, de-identified trial data and associated metadata will be stored 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.

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.

36 DATA SHARING

Requests for access to study data should be made to the Chief Investigator, including the purpose for the request. The Chief Investigator will then follow the applicable Sponsor policies and study data sharing plan in determining if data can be provided. A response to the requestor will be made within 90 days of receipt of the request.

37 REFERENCES

1. **Cooper C, Dennison EM, Leufkens HGM, Bishop N, Staa TP van**. Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Miner Res Off J Am Soc Bone Miner Res* 2004;19(12):1976–1981.

2. **Peterson CA, Peterson HA**. ANALYSIS OF THE INCIDENCE OF INJURIES TO THE EPIPHYSEAL GROWTH PLATE: *J Trauma Inj Infect Crit Care* [Internet] 1972 [cited 6 Jul 2020];12(4):275–281.

3. **Govilkar S, Bolt A, Ford D, Kiely N**. Reviewing Current Concepts in Distal Tibial Physeal Injuries: New Twists and Old Turns? *Orthop Muscular Syst* [Internet] 2018 [cited 23 Jun 2020];07(02).

4. **Barmada A, Gaynor T, Mubarak SJ**. Premature physeal closure following distal tibia physeal fractures: a new radiographic predictor. *J Pediatr Orthop* 2003;23(6):733–739.

5. **Russo F, Moor MA, Mubarak SJ, Pennock AT**. Salter-Harris II Fractures of the Distal Tibia: Does Surgical Management Reduce the Risk of Premature Physeal Closure? *J Pediatr Orthop* 2013;33(5):524–529.

6. **Asad WA, Younis MHS, Ahmed AF, Ibrahim T**. Open versus closed treatment of distal tibia physeal fractures: a systematic review and meta-analysis. *Eur J Orthop Surg Traumatol Orthop Traumatol* 2018;28(3):503–509.

7. **Berson L, Davidson RS, Dormans JP, Drummond DS, Gregg JR**. Growth Disturbances After Distal Tibial Physeal Fractures. *Foot Ankle Int* 2000;21(1):54–58.

8. **Kraus R, Kaiser M**. Growth Disturbances of the Distal Tibia after Physeal Separation – What Do We Know, What Do We Believe We Know? A Review of Current Literature. *Eur J Pediatr Surg* 2008;18(05):295–299.

9. **Leary JT, Handling M, Talerico M, Yong L, Bowe JA**. Physeal Fractures of the Distal Tibia: Predictive Factors of Premature Physeal Closure and Growth Arrest. *J Pediatr Orthop* 2009;29(4):356–361.

10. **Park H, Lee DH, Han SH, Kim S, Eom NK, Kim HW**. What is the best treatment for displaced Salter–Harris II physeal fractures of the distal tibia? *Acta Orthop* 2018;89(1):108–112.

11. **Binkley A, Mehlman CT, Freeh E**. Salter–Harris II Ankle Fractures in Children: Does Fracture Pattern Matter? *J Orthop Trauma* 2019;33(5):e190–e195.

12. **Rohmiller MT, Gaynor TP, Pawelek J, Mubarak SJ**. Salter-Harris I and II Fractures of the Distal Tibia: Does Mechanism of Injury Relate to Premature Physeal Closure? *J Pediatr Orthop* 2006;26(3):322–328.

13. **Spiegel PG, Cooperman DR, Laros GS**. Epiphyseal fractures of the distal ends of the tibia and fibula. A retrospective study of two hundred and thirty-seven cases in children. *J Bone Joint Surg Am* 1978;60(8):1046–1050.

14. **Kling TF, Bright RW, Hensinger RN**. Distal tibial physeal fractures in children that may require open reduction. *J Bone Joint Surg Am* 1984;66(5):647–657.

15. **Chadwick CJ, Bentley G**. The classification and prognosis of epiphyseal injuries. *Injury* 1987;18(3):157–168.

16. **Perry DC, Wright JG, Cooke S, Roposch A, Gaston MS, Nicolaou N, et al.** A consensus exercise identifying priorities for research into clinical effectiveness among children's orthopaedic surgeons in the United Kingdom. *Bone Amp Jt J* 2018;100-B(5):680–684.

17. **Morgan EM, Mara CA, Huang B, Barnett K, Carle AC, Farrell JE, et al.** Establishing clinical meaning and defining important differences for Patient-Reported Outcomes Measurement Information System (PROMIS(®)) measures in juvenile idiopathic arthritis using standard setting with patients, parents, and providers. *Qual Life Res* 2017;26(3):565–586.

18. **Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware Jr. JE**. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol* 2014;67(5):516–526.

19. **Leo DG, Perry DC, Abdullah B, Jones H**. PROMIS Paediatric Mobility tool is correlated with accelerometer-measured physical activity in children with hip diseases. *Bone Jt J* [Internet] 2021 [cited 23 Feb 2021];103-B(2):405–410.

20. **Wong DL, Baker CM**. Pain in children: comparison of assessment scales. *Pediatr Nurs* 14(1):9–17.

21. **Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, et al.** Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19(6):875–886.

22. **Eidt-Koch D, Mittendorf T, Greiner W**. Cross-sectional validity of the EQ-5D-Y as a generic health outcome instrument in children and adolescents with cystic fibrosis in Germany. *BMC Pediatr* BioMed Central, 2009;9(1):55.

23. **Neelly K, Wallmann HW, Backus CJ**. Validity of measuring leg length with a tape measure compared to a computed tomography scan. *Physiother Theory Pract* [Internet] 2013 [cited 18 Nov 2020];29(6):487–492.

24. **Marson BA, Manning JC, James M, Craxford S, Deshmukh SR, Ollivere BJ**. CORE-Kids: a protocol for the development of a core outcome set for childhood fractures. *BMJ Open* [Internet] 2020 [cited 6 Jul 2020];10(2):e036224.

25. **Parsons N, Parsons N, Odumenya M, Odumenya M, Edwards A, Edwards A, et al.** Modelling the effects of the weather on admissions to UK trauma units: a cross-sectional study. *Emerg Med J* 2011;28(10):851–855.

26. **Royal College of Emergency Medicine (UK)**. Best Practice Guideline. Management of Pain in Children. 2013.

27. **Thissen D, Liu Y, Magnus B, Quinn H, Gipson DS, Dampier C, et al.** Estimating minimally important difference (MID) in PROMIS pediatric measures using the scale-judgment method. *Qual Life Res* 2016;25(1):13–23.

28. **Yost KJ, Eton DT, Garcia SF, Cella D**. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol* 2011;64(5):507–516.

29. **Wright JG**. The minimal important difference: who's to say what is important? *J Clin Epidemiol* 1996;49(11):1221–2.

30. **Vickers AJ**. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol* [Internet] 2001 [cited 18 Nov 2020];1(1):6.

31. **National Institute for Health and Care Excellence**. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence (NICE), 2013.

32. **Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al.** Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* [Internet] 2013 [cited 14 Jul 2020];346(mar25 1):f1049–f1049.

33. Home :: DIRUM - Database of Instruments for Resource Use Measurement. http://www.dirum.org/ , (date last accessed 2 December 2019).

34. **Mihaylova B, Briggs A, O'Hagan A, Thompson SG**. Review of statistical methods for analysing healthcare resources and costs. *Health Econ* 2011;20(8):897–916.

35. **Manca A, Hawkins N, Sculpher MJ**. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14(5):487–496.

36. **Moe-Byrne T, Knapp P, Perry D, Achten J, Spoors L, Appelbe D, 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* [Internet] 2022 [cited 21 Jul 2022];12(7):e057508.

38 VERSION HISTORY

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

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the protocol
2.0	31Jan2024	**Section 10.1.2**: Removal of 'recruitment centre' from stratification factors in (left in in error)
3.0	15Feb2024	**Sections 10.8**, **28.4** and **35.1**: Amendment to retention period of identifiable data. Addition of ISRCTN number

APPENDIX 1 – STUDY FLOW CHART