The Big BOSS Study- The British Orthopaedic SCFE Surgery Study for Severe Stable Slips.

A multi-centre prospective randomised superiority trial of an acute deformity correction versus pinning in-situ for severe stable SCFE in children

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I declare no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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2. LAY SUMMARY

Why this research?

A Slipped Capital Femoral Epiphysis or SCFE is a rare condition but one of the most important children's and adolescent hip disorders. SCFE is the most common reason for hip replacement surgery in both adolescence and early adulthood, and the number of children and young people with this condition is increasing. A survey of almost 100 surgeons from the British Society for Children's Orthopaedic Surgery have prioritised this as requiring urgent research.

The simplest explanation of the disease is to imagine the hip like a ball of ice cream (the top of the hip) on an ice cream cone (the thigh bone). As a result of the disease, the ice cream ball could melt and slip a little away from the cone (minor slip) or slip a lot (severe slip) or could just come loose from the cone completely (unstable slip). Unstable slips are particularly worrisome as the supply of blood, which gives the bone nutrition and oxygen to remain healthy, could stop completely, which may cause the whole hip to die (with the ice cream ball becoming very squashed).

The treatment of SCFE always involves surgery to stabilise the slip, however which type of surgery is necessary depends on how bad the slip is. In mild slips, surgery involves inserting a screw using keyhole surgery, to stop the hip slipping any more (this is called 'stabilising'). For severe slips, where the hip bone is most deformed, doctors currently can choose between two types of operation and it is not clear whether one is better than the other. The first treatment option is inserting a screw through keyhole surgery (stabilising but not putting the ice cream back on the cone) and accepting that the shape of the hip has changed. This may cause problems with walking and may risk later osteoarthritis. The second option is to correct the slip through major surgery (stabilising and putting the ice cream back on the cone), though this could make the hip unstable and carries a risk that the hip bone may disintegrate (i.e., a very squashed ice-cream) causing disability.

What question are we hoping to answer with this study?

When children between 8 and 15 years old have a severe stable SCFE, is major surgery to correct and protect the hip better than keyhole surgery which protects the hip but does not correct the shape?

What sort of study is it?

This study is called a trial, which is the best and fairest way to compare treatments. In this study which is called the British Orthopaedic SCFE Surgery Study for Severe Stable Slips (Big BOSS Study), half the children and young people who take part will have major surgery to correct the shape of the hip bone and stabilise the hip, whilst the other half will have keyhole surgery to stabilise the hip without correcting the shape. Parents/guardians and children won't be able to choose which treatment they get, as this will be allocated fairly using a process called randomisation.

How many children will be involved?

We plan to include at least 192 children over a three-year period from approximately 30 UK hospitals. 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 aged between 8 and 15 years old with a Stable Severe SCFE will be asked to join the study.

Those who agree to join the study, with the support of their families, will be split into two groups, using a research process called 'randomisation' to fairly allocate treatments:

1. MAJOR SURGERY –children will have an operation under a general anaesthetic. Whilst asleep, children have surgery to correct the shape of the hip bone associated with the SCFE. The hip will then be stabilised with a screw(s) to protect against future SCFE.

2. KEYHOLE SURGERY - children will have an operation under a general anaesthetic. Whilst asleep, children have surgery to stabilise the hip with a screw(s) to protect against worsening SCFE. Surgeons will not attempt to correct the shape of the hip associated with the SCFE.

All children and young people will be followed-up for two-years to monitor their hip. They will also be asked about pain, if they needed any more surgery, school attendance, any complications, the number of hospital visits, their quality of life and satisfaction with care.

How will this research make a difference?

At the end of the study, it 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 parents and children and will be invited to share their experience of the trial and the results with medical professionals.

Has there been involvement from families when this research was set up?

Families have been involved over several years through a preceding study – called the BOSS Cohort Study. Emma Morley has been a keen parent co-investigator throughout the last 5 years. Milli Browne was a participant in the BOSS Cohort, following a Severe Stable SCFE. Both are keen co-investigators in BigBOSS. The research has been discussed with children and families affected by the condition and the Young Person’s and Parent's Advisory Groups in Liverpool.

3. SYNOPSIS

Study Title	British Orthopaedic SCFE Surgery Study for Severe Stable Slips		
Acronym	Big BOSS		
Study Registration	The study has been registered with the current controlled trials database under reference number ISRCTN59719122 NIHR CRN Portfolio: 55962		
Sponsor	Alder Hey Children's NHS Foundation Trust		
Funder	National Institute for Health and Care Research (NIHR131176) HTA Programme		
Study Design	Multi-centre prospective randomised superiority trial		
Study Participants	Children aged 8 to 15 years with a Severe Stable SCFE		
Planned Sample Size	A minimum of 192 patients.		
	Objectives	*Outcome Measures*	*Time Point*
Primary	To determine whether children treated with acute correction have improved function compared with children treated with pinning in-situ, measured using observed differences in the PROMIS Mobility Score for Children at two-years post-randomisation.	PROMIS-Mobility	Baseline, 24 months post-randomisation
Secondary	To quantify and draw inferences in the following outcomes between treatment group during the first two-years post randomisation:		
	i) **function** using the PROMIS-Mobility Score.	PROMIS-Mobility	Baseline, 8 weeks, 3, 6 and 12 months post-randomisation
	ii) **pain scores** using the Wong-Baker faces pain rating scale.	Wong-Baker Faces Pain Score	Baseline, 8 weeks, 3, 6, 12 and 24 months post-randomisation
	iii) **quality of life** using EQ-5D-Y.	EQ-5D-Y	Baseline, 8 weeks, 3, 6, 12 and 24 months post randomisation
	iv) **satisfaction with care**.	Satisfaction score	8 weeks, and 24 months post-randomisation

	v) **educational participation** recording educational absences.	Bespoke 'days of missed educational attendance' questionnaire	8 weeks, 3, 6, 12 and 24 months post-randomisation
	vi) **cost-effectiveness** of the treatments to the NHS and the broader economy.	Healthcare and personal resource use, absence from work, purchased childcare and EQ-5D-Y	8 weeks, 3, 6, 12 and 24 months post randomisation
	vii) **the complication rate** including avascular necrosis, re-slip and the need for further operative treatment.	Parent and site reported Complications record	8 weeks, 12 and 24 months post randomisation
Intervention	Acute correction		
Comparator	Pinning in-situ		

4. ABBREVIATIONS

AVN	Avascular Necrosis
BOSS	British Orthopaedic Surgery Surveillance
BSCOS	British Society of Children's Orthopaedic Surgery
CAT	Computer Adaptive Test
CHI	Community Health Index (number)
CI	Chief Investigator
CRAFFT	Children's Radius Acute Fracture Fixation Trial
CRF	Case Report Form
DOB	Date of Birth
DSMC	Data and Safety Monitoring Committee
EQ-5D-Y	EuroQol - Youth
FAI	Femoro Acetabular Impingement
FORCE	Forearm Fracture Recovery in Children Evaluation
GCP	Good Clinical Practice
H&C	Health and Care (number)
HE	Health Economy/Economist
HRA	Health Research Authority
HTA	Health Technology Assessment
MCID	Minimally Clinically Important Difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institute for Health
NIHR	National Institute For Health and Care Research
NAHR	Non-Arthroplasty Hip Registry
OCTRU	Oxford Clinical Trials Research Unit
PACS	Picture Archiving and Communication System
PAG	Parents Advisory Group
PI	Principal Investigator
PPI	Personal And Public Involvement
PROMIS	Patient Report Outcomes Measurement Information System
SCIENCE	Surgery or Cast for Injuries of the EpicoNdyle in Children's Elbows
QALY	Quality-Adjusted Life Year
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCFE	Slipped Capital Femoral Epiphysis
SUFE	Slipped Upper Femoral Epiphysis
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

5. BACKGROUND AND RATIONALE

Slipped Capital Femoral Epiphysis (SCFE) (also known as a Slipped Upper Femoral Epiphysis (SUFE)) is the most common hip disease of adolescence, akin to a hip fracture. Children typically present with knee, thigh or hip pain, or a limp[1]. It principally affects children between 10 and 14 years old, with a similar preponderance in boys and girls. There is strong evidence that childhood obesity is the major cause[2]. In the short-term it always requires surgery to stabilise the femoral head onto the femoral neck, and typically results in deformity at the level of the growth plate, which lies between the head and the neck of the femur. In the long-term, SCFE accelerates the development of osteoarthritis, and many patients have disability necessitating hip replacement in early adulthood[3].

Despite SCFE being the most common hip disease of adolescence, robust evidence to support effective management and intervention is poor, with no clinical trials to guide treatment decisions. Consequently, treatment strategies vary by country, by hospital and even by surgeon[4,5]. The most important prognostic classification in SCFE is based on whether the child is able to walk at presentation to hospital; termed "stability". If a child can walk at the point of presentation, with or without the use of crutches or supports, the hip is deemed 'stable' and has a negligible risk of avascular necrosis (AVN)[6]. If the child cannot walk, the hip is deemed 'unstable' with an AVN rate up to 47%[6]. AVN is the process whereby the hip loses its blood supply and collapses which almost inevitably causes profound pain and disability; usually necessitating an expedited hip replacement. AVN occurs because the vessels to the femoral head are easily injured owing to a tenuous blood supply to the head of the femur.

In addition to 'stability', SCFE is also classified by how much the bone has 'slipped' out of place, with 'severe slips' being those with marked deformity causing abutment of the head of the femur onto the acetabulum; described as femoroacetabular impingement (FAI). FAI can cause pain, and is believed to cause premature osteoarthritis[7], albeit less acutely than AVN.

Slips that are 'Stable' with 'Severe' deformity (severe stable SCFE) cause the most controversy with regards to management. These are 'stable' and therefore at a low risk of AVN, but the FAI can cause marked pain and disability in childhood.

5.1. CURRENT PRACTICE

Traditionally, the approach to managing a severe stable SCFE is to immediately stabilise the hip with a minor procedure, albeit accepting the FAI. If later the child becomes symptomatic, then surgical treatments to alleviate symptoms may be offered. It is then ensured that subsequent surgery (i.e., an intertrochanteric osteotomy) avoids the region with tenuous vasculature in the femur, thereby minimising the risk of AVN. However, this surgery realigns the femur by creating a secondary deformity, thus not restoring the normal anatomy of the femur. Newer techniques have created a wave of interest in hip surgery at the site of the initial deformity[8], enabling an acute correction. These newer techniques restore normal anatomy and prevent impingement, which may reduce the risk of arthritis and hip replacement. However, they involve much more major surgery to acutely correct the deformity, though doing this through the area with tenuous vasculature, risking disabling AVN[9]. Surgeons are faced a dilemma whether they should attempt to surgically correct the shape of the hip, though risking AVN and femoral head collapse, or accept the FAI with the resulting pain and disability.

The adoption of the newer technique is increasingly widespread with recent studies, albeit with low quality evidence, recommending this approach as first-line treatment in Severe Stable SCFE[10,11]. However, the

National Institute of Health and Clinical Excellence reviewed Severe Stable SCFE in 2015, and noted significant safety concerns related to the newer surgical techniques[12]. Controversy related to the optimal approach is ongoing.

Whilst surgeons have been keen to advance this research area, the knowledge of SCFE up to now has not been sufficiently mature to allow a trial to be successful - i.e., even the incidence of SCFE, and the frequency of subtypes was uncertain. In 2016 the British Orthopedic Surgery Surveillance (BOSS) Study began, which was a data-enabled nationwide observational study of new cases of SCFE. This study collected surgeon reported outcomes on almost all new cases of SCFE across the UK in an 18-month period (April 2016 – Sept 2017). The vast majority of hospitals treating SCFE in the Great Britain agreed to participate (143 of 144 UK hospitals). Monthly routine data downloads (i.e., Hospital Episode Statistics, Scottish Morbidity Record, Patient Episode Database for Wales) were used to ensure completeness of case ascertainment by matching cases by hospital, age, gender and date of surgery. The IT system developed to manage this automatically notified surgeons of potential missing cases, and invited surgeons to either enter cases, or confirm that the diagnosis in routine data was erroneous (i.e., removal of metal for previously treated SCFE). Almost 95% of cases identified within Hospital Episode Statistics had surgeon-reported information collected, including disease severity, stability and treatments. In total, the BOSS study identified 486 new cases of SCFE across the UK, of which 187 cases were potentially eligible to be recruited to this study (i.e., stable and severe causing significant femoroacetabular impingement). Of these 187 cases, they were primarily referred and treated in the specialist hospitals that have contributed to this application. Within this observational cohort, surgical and radiographic follow-up was available for 88% of cases at 2 years.

The current practice was evenly split between the two interventions; with half of hospitals opting to acutely reduce these hips (44%), and half opting to pin the hip in-situ (46%). The remainder of cases (5%) used a slightly different approach permitting growth of the hip to attempt to resolve the deformity. Whilst BOSS was not a trial, it did demonstrate in stable hips that open reduction of the hip was an independent risk factor for AVN (OR 7.5 (95% CI 2.4 – 23.4)). On the counter side, it demonstrated that 7 hips treated without open reduction had extra-capsular realignment osteotomies by 2 years, and 8 hips had undergone arthroscopic debridement.

The patient reported outcomes measures available in the BOSS Study showed evidence that measures of physical health were the most sensitive to change in the SCFE population. It also demonstrated that at 2 years, only 53% of these adolescents reported very good or excellent physical function, indicating the degree of ongoing disability resulting from SCFE regardless of the initial management.

5.2. WHY IS THIS IMPORTANT?

The growing uncertainty amongst surgeons regarding the optimal surgical approach has prompted members of the British Society of Children's Orthopedic Surgery (BSCOS) to prioritise this question as their most important research priority[13]. Similarly, a James Lind Alliance Priority Setting Partnership has also highlighted the importance of this question[14]. This study has received formal support from the BSCOS.

Furthermore, there is strong evidence to suggest that SCFE is caused by childhood obesity[2], and there is suggestion that rates of SCFE are rising as global obesity increases[15]. The WHO report on ending childhood obesity highlighted a lack of awareness of the consequences of obesity[15].

The surgical management of severe stable SCFE has altered in recent years, without any robust evidence to support this change. New surgical strategies may have devastating complications for some children. Determining the optimal surgical management of severe stable SCFE is important to limit the profound disability that may occur as a consequence of this disease.

6. OBJECTIVES AND OUTCOME MEASURES

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

The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost-effectiveness of acute correction of deformity, compared to pinning in-situ for the management of severe stable SCFE in children.

Table 1: Objectives and Outcome Measures

Objectives	**Outcome Measures**	**Time point(s) of evaluation of this outcome measure**
To determine whether children treated with acute correction have improved function compared with children treated with pinning in-situ, measured using observed differences in the Patient Reported Outcomes Measurement Information System Mobility Score for Children at two-years post-randomisation.	PROMIS-Mobility	Baseline, 24 months post-randomisation
To quantify and draw inferences in the following outcomes between treatment group during the first two-years post randomisation: i) **function** using the PROMIS-Mobility Score.	PROMIS-Mobility	Baseline, 8 weeks, 3, 6 and 12 months post-randomisation
ii) **pain scores** using the Wong-Baker faces pain rating scale.	Wong-Baker Faces Pain Score	Baseline, 8 weeks, 3, 6, 12 and 24 months post-randomisation
iii) **quality of life** using EQ-5D-Y.	EQ-5D-Y	Baseline, 8 weeks, 3, 6, 12 and 24 months post-randomisation
iv) **satisfaction with care** using a Likert scale	Satisfaction score	8 weeks, and 24 months post-randomisation
v) **educational participation** recording educational absences.	Days of missed educational attendance	8 weeks, 3, 6, 12 and 24 months post-randomisation

vi) **cost-effectiveness** of the treatments to the NHS and the broader economy.	Healthcare and personal resource use, absence from work, purchased childcare and EQ5D-Y	8 weeks, 3, 6, 12 and 24 months post randomisation
vii) **the complication rate** including avascular necrosis, re-slip and the need for further operative treatment.	Complications	8 weeks, 12 and 24 months post randomisation

6.1. OUTCOME MEASURES

Given the age of participants, patient reported outcomes will generally be self-reported by participants, with the exception of items relating to health resource use and satisfaction with care, which will be answered by the parent or with the help of the parent(s). A schedule outlining the timelines for data collection can be found in Table 1.

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 [16,17]. PROMIS-CATs have been successfully implemented in other NIHR-HTA trials led by the lead investigator, including FORCE IRAS 246654[18], CRAFFT IRAS 264593 and SCIENCE IRAS 259931. 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 in collaboration with the NIH. These tools can be administered to healthy children as well as to those with a variety of chronic health conditions. The PROMIS Paediatric item banks were developed using a strategic item generation methodology adopted by the PROMIS Network utilising item response theory. Field-testing occurred among 4129 children aged 8 – 17 years. Lower T-scores indicate a worse outcome function. PROMIS mobility is available in full, short-form or as a computer adaptive test 'CAT' (average 8-questions). A CAT enables the answer from one question to inform the choice of the next and so each child could answer a distinct set of questions to arrive at their score. 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

The Wong-Baker faces pain score [20] is a validated self-reported tool that will be self-reported amongst all children in the trial. 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[21].

EQ-5D-Y

This 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 especially adapted in terms of language for use amongst children, with both proxy and self-reported versions.[22,23] Given the age of participants within this trial, 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 Big BOSS 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 complications will be recorded. The complications anticipated in the management of these patients (including readmission/ reoperation to address them) include pressure sores, non-union of the bone, wound or bone infection, injury/irritation to nerves altering sensation to the lower limb or toes, the need to remove/adjust metal pin/screws (planned or unplanned) (i.e. screw cut out or backing out (metalwork displacement)), heterotopic bone formation, dislocated hip, avascular necrosis, chondrolysis, re-slip (i.e., Recurrence of SCFE) and implant-related fracture. Any digital images of the hip/pelvis that have been collected as part of routine practice will be harvested from PACS at the end of the trial. In particular, we will seek to identify images collected pre-operatively, intra-operatively (where relevant) and the last available follow-up image (i.e., the most recent image collected prior to the 2-year primary outcome point - although we acknowledge that this may have been some weeks/months prior to this time-point). No specific imaging is required at any stage as part of the protocol for this trial. Collection of routine digital images as described above has been reviewed by Health Research Authority (HRA) Radiation Assurance review who indicated that the harvesting of routine images in this manner does not constitute exposure to radiation – passing their test "if the radiographs were not available, would the PI require that they took place".

Resource use

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

Satisfaction with care

The perception of satisfaction with care will be collected using a Likert Scale. This will be completed by parents.

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.

6.2. CHOICE OF PRIMARY OUTCOME MEASURE

PROMIS-Mobility CAT is the only validated tool to assess lower extremity function in children. We have demonstrated the PROMIS mobility score in children correlates well with physical function measured using an accelerometer[19]. See section 6.1.

6.3. USE OF CORE OUTCOME SETS

There are no core outcome sets that address SCFE.

7. TRIAL DESIGN

7.1. SUMMARY OF RESEARCH

The proposed 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.

7.1.1 Internal Pilot

The pilot will take place at a minimum of 20 centres over 12 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 kept at 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.

Stop-go criteria (Table 2) will be reviewed at 12 months after the study opens to recruitment. The stop-go criteria are based on recruitment rate, sites open, participants recruited, and participants received randomised treatment, with the poorest performing of the four parameters defining the action required to be taken.

Table 2: Stop-Go Criteria for Internal Pilot Phase

Progression guidance	Stop-Go Criteria
Continue with study – no action required	**GREEN** • Average recruitment rate/site/month >0.20 • Number of sites opened: 20 • Participants received randomised treatment: ≥80% • ≥49 participants recruited would clearly indicate success.

Progression guidance	Stop-Go Criteria
Continue with study – action required: • Review recruitment strategies and modify/monitor closely • Discuss strategies with the TSC and funder.	**AMBER** • Average recruitment rate/site/month 0.1 to 0.2 • Number of sites opened: 11-19 • Participants received randomised treatment: 60-79% • ≥24 participants would clearly indicate action is required.
Review with funder	**RED** • Average recruitment rate/site/month: <0.1 • Number of sites opened: ≤10 • Participants received randomised treatment: <60% • <24 participants would clearly indicate significant challenges.

When all criteria are green at the end of the feasibility phase and recruitment is equal to or above 49, we will present a report to the Trial Steering Committee (TSC) and continue with recruitment.

If one or more criteria are amber, but none are red, and recruitment is equal to or above 24 we will provide the TSC with a report containing a number of strategies, such as increasing the number of UK sites, closer monitoring of sites or using incentives, to enhance recruitment/compliance throughout the main phase of the study. Decisions on how to proceed will be dependent on the recommendation from the TSC and funder.

If one or more criteria are red, and recruitment is below 24 we propose to meet with representatives from the funder to consider feasibility and discuss the future of the trial. It would also allow for a discussion around more substantial changes such as potential changes to eligibility or inclusion of international recruiting centres.

Optimisation of the recruitment procedures will take place through an integrated qualitative study – the *Big BOSS Information Study*. This will explore communication about the trial and the acceptability of the trial to families. It will also explore the views of recruiting staff on trial recruitment and the views of staff from sites who have declined to participate in the trial. The findings will be used to enhance trial procedures and information for patients, their parents and healthcare professionals.

7.1.2 Trial Structure

All children aged 8-15 years inclusive presenting to the recruitment centres with a severe stable SCFE are potentially eligible to take part.

After informed consent/assent has been given, 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 *pinning in-situ* or *acute correction* using a computer-based randomisation system.

After treatment, the parents and/or participants will be asked to complete further questionnaires at 8 weeks, 3 months, 6 months, 12 months and 24 months post-randomisation.

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

8. PARTICIPANT IDENTIFICATION

8.1. TRIAL PARTICIPANTS

The target population is children aged 8 to 15 years inclusive who present with a severe stable SCFE.

8.2. INCLUSION CRITERIA

Patients can be included for this trial if:

- They are aged 8 to 15 years old inclusive.
- There is radiographic evidence of a SCFE.
- The child is able to walk with or without the use of crutches or walking aids (i.e., the SCFE fulfils the 'Loder' definition of 'Stable').
- The magnitude of the SCFE is severe; such that the treating clinician believes that it will cause significant femoroacetabular impingement.

Note: Patients with opposite SCFE that is concurrent (new) or occurred previously (old) may be included (as long as they have not previously been included in the BigBOSS study). If the opposite sided hip is concurrent (i.e. new), the most severe hip will be considered the hip of interest.

8.3. EXCLUSION CRITERIA

Patients will be excluded from participation in this trial if:

- 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 Big Boss Study.

9. PROTOCOL PROCEDURES

9.1. DATA COLLECTION

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 trial treatments.

After the allocated treatment has been provided, the research team will complete a treatment form (see Table 3).

Follow-up clinical data (i.e., a routine records check related to planned and unplanned care) will be collected at 8 weeks, 12 months and 24 months post-randomisation.

Table 3 Site data collection time points

Procedures	Screen	Baseline	Clinic visit at 6-8 weeks	12 month clinic	24 month clinic
Assessment of Eligibility Criteria (Screening log)	X				
Informed Consent +/- Assent	X				
Trial intervention (Treatment CRF)		X			
Site Follow-Up CRF			X	X	X
Routinely Collected PACS Image Harvest (as available)					X

For follow-up participant data, parents and/or participants will be prompted to complete online questionnaires at 8 weeks, 3, 6, 12 and 24 months post-randomisation. Questionnaires will generally be self-reported, however parent input will be advised when completing resource use, additional care, educational absence and satisfaction with care questionnaires (see Table 4). A direct link to the on-line questionnaire will be sent via a text message or email. If the parent and/or participant have not responded to the initial and reminder messages within a specified timeframe (as outlined in the data management plan), or if the central trial team have queries relating to data that has been entered by the parent and it is not appropriate for the recruitment centre 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 trial team at the University of Oxford.

Table 4 Participant data collection time points

Data collected	Screen	Baseline	8 weeks	3 months	6 months	12 months	24 months
Informed Consent +/- Assent	X						
Demographic data and medical history	X						
PROMIS Mobility		X	X	X	X	X	X
EQ-5D-Y		X	X	X	X	X	X
Wong Baker Pain Score		X	X	X	X	X	X
Likert satisfaction with care			X				X
Educational Participation			X	X	X	X	X
Resource Use			X	X	X	X	X
Complications			X			X	X

If the family indicates that a complication or additional surgery has occurred, recruitment centres will be prompted to complete a complication form to give full details of the event.

9.2. RECRUITMENT

Patients will be screened from acute admissions and/or fracture clinics at the recruitment centres. All patients aged 8-15 years (inclusive) with SCFE 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 patients not being randomised. The screening logs will contain non-identifiable information such as the patient's age, height, weight and injury severity, which will allow for an assessment of the generalisability of the trial. In addition, information on ethnicity and a deprivation score (based on the postcode of the patient's main home address) will be collected to monitor inclusivity into research in line with the NIHR-INCLUDE guidance. We believe that, unlike children's trauma, there is no significant seasonal variation in SCFE in children.

9.2.1 *Big BOSS Information Study*

Recruitment of patients to surgical trials can be challenging. Given the rarity of SCFE it is especially important to optimise recruitment strategies. A qualitative study, the *Big BOSS Information Study*, will be embedded during the pilot phase to address recruitment challenges and inform strategies to enhance communication and recruitment as we and others have demonstrated in previous trials[25,26].

Information generated from the *Big Boss Information Study* will be used to develop practical strategies that can be implemented in the main trial to improve recruitment and enhance acceptability of the trial, which may include changes to the presentation or delivery of trial information. We will further use the qualitative findings to understand: i) staff experience of being invited to join, and being involved in a paediatric surgical trial, ii) parent and children's experience of being asked to participate in a randomised controlled trial, and, iii) children's experience of the injury, treatment and its consequences in their daily life. Parent and children's experience of recruitment will help inform future studies.

Qualitative data will be collected in up to 15 sites and comprise transcribed audio recordings of: trial recruitment/consent consultations (N=30) between families and surgeons; follow-up in-depth semi-structured qualitative interviews with a purposive sample of families invited to participate in the study (20 patients, 20 parents and 15 staff involved in recruiting participants). Further qualitative data will be collected from staff at non-participating sites to explore their reasons for feeling unable to be part of the trial (15 staff).

Purposive sampling for audio recorded consultations and interviews will aim for data saturation and encompass diversity in terms of patient demographics, trial site and treatment allocation. A subset of patients, parents and surgeons/staff who decline the trial will also be interviewed. Interviews will be conversational and explore: perceptions of the trial, the recruitment processes/information materials and suggestions for improving these; views and experiences of deciding whether to participate, treatment preferences; experiences of the treatment interventions and recovery. Interview topic-guides will be developed in collaboration with PPI partners and adapted as appropriate to patients, parents and health professionals. We will use games and other techniques to support the engagement of younger patients in interviews. Participants will be interviewed either face-to-face or via video-conference/ telephone according to participant preference. Children and young people can choose if they wish to be interviewed alone, or with their family present.

Thematic analyses of transcribed audio recorded consultations and interviews will identify the

circumstances, topics or phrases that are associated with recruitment and communication difficulties[27,28]. A key focus will be comparing i) what patients/parents and health professionals 'said' during recruitment consultations with ii) the messages they 'heard' as reported in interviews. This will identify how to enhance clarity and balance in communication about the trial and the interventions. Clinical team members and patient co-investigators will be involved in reviewing the emerging findings and in developing feedback for sites. A key focus for staff interviews at non-participating sites will be the exploration of factors for why they were unable to join the trial. We will work collaboratively with sites in developing practical strategies to enhance recruitment and consent. Based on the cumulative lessons learnt we will also produce training resources to optimise recruitment and consent in the main trial. This "Quintet" style approach has demonstrated its value in enhancing recruitment and informed consent in previous trials, including paediatric trials[25,29].

9.3. INFORMED CONSENT

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. At the start of this conversation verbal permission will be taken for the recruitment discussion to be audio-recorded in sites taking part in the Information Study. Participation in the *Big BOSS Information Study* is independent of the main Big BOSS study and all families approached about the Big BOSS study will be eligible for the audio recording, including those who subsequently decline the Big BOSS study.

If the family is interested in potentially participating in the Big BOSS study, 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 trial procedures. Age-appropriate written information is also available to be downloaded and/or printed – though our parent and child advisors are keen that these are only printed when necessary, being mindful of the carbon footprint.

After the information is delivered, the family will be given the opportunity to discuss issues related to the trial with the research team, the treating clinician, and family and friends. The individual seeking consent will ensure that the patient and parent have fully understood the information provided and are willing to consent / assent. The parent will then be asked to sign an electronic informed consent form. All children will also be asked to provide their assent by signing an electronic assent form. At this time, consent will also be sought to retain the audio recording of the recruitment conversation for transcription and analysis as part of the *Big Boss Information Study*. If consent to keep the audio recording is not provided, then the recording will be deleted.

There are circumstances where the recruiting 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 minor expresses a wish for the decision to be made solely by their parent. Therefore, the absence of assent does not exclude the patient from the trial 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, the child will not be included in the trial. A copy of all electronic consent and assent forms will be emailed to the parent directly. If the parent does not have an email address, the local research team will download and print a copy of the completed consent/assent forms to give to the parent.

Participants who turn 16 years of age prior to the collection of the final 2-years 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.

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.

Any new information that arises during the trial 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.

9.3.1 Consent for data linkage with the Non-Arthroplasty Hip Registry

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

9.3.2 Consent for *Big BOSS Information study*

As outlined above, clinical staff will seek verbal permission to audio record their consultations with patients and families who they approach about the trial. This is a process that we have used in previous surgery studies involving children[24]. The purpose of the audio recording will be briefly outlined, and a recording device activated if the family give permission. At the end of the consultations, clinical/ research staff will discuss the *Big Boss Information Study* with patients/families in more detail and seek signed consent (via the Big BOSS electronic consent system) for transcripts of the audio recording to be included in the analysis. Audio recordings from patients/families who decline inclusion of their consultation data in the *Big Boss Information Study* will be erased at the end of the consultation.

For interviews, members of the research team will collect consent from the parent to pass their contact details to the *Big Boss Information Study* team through the main trial electronic consent system. An experienced qualitative researcher from the *Big Boss Information Study* will subsequently contact families to explain the *Big Boss Information Study* further and invite them to be interviewed and seek their consent. For both face to face and phone/video-conference interviews, electronic consent/assent will be sought, with a backup paper system when electronic means is not available (i.e. no access to the internet or email). When interviews are conducted by phone/video-conference and electronic consent is not available, we will collect verbal consent/assent as this will reduce additional paperwork and burden for participants. This will involve the researcher reading each aspect of the *Big BOSS Information Study* Interview consent/assent form to participants and checking/confirming each response on the consent form as the participant provides verbal consent. The researcher will add the participant's name, date and 'interview' where the signature is required and will post/email a copy of the form to the participant (based on participant preference). Consent discussions will be audio recorded (separately from the main interviews) for auditing purposes.

9.4. RANDOMISATION

The patient will be randomised after consent and baseline data have been obtained. 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.

Consented participants will be randomised to one of two intervention groups (1:1) using a remote computer randomisation service provided by the University of Oxford. Randomisation allocation will be implemented using a minimisation algorithm with stratification factors: age group (8-10 years, 11-15 years) and current/previous opposite sided SCFE (presence or absence). The minimisation algorithm will be seeded with a number of allocations and a non-deterministic probabilistic element will be introduced in order to prevent predictability of the treatment allocation.

Stratification by participant age will ensure balance (8-10 years and 11–15 years), because younger children have better remodelling capacity than older children and therefore potentially different long-term sequela.

Stratification by presence or absence of current or previously fixed opposite sided SCFE will ensure that functional restrictions related to the opposite hip, which is likely to affect approximately 20% of participants[30], is balanced between the groups.

The most severe hip is the unit of randomisation and assessment during the trial. The surgical management of the opposite hip will be at the discretion of the surgeon.

9.5. BLINDING AND CODE-BREAKING

Participants and their parents cannot be blinded to their treatment. The treating clinician also cannot be blinded to the treatment they are providing.

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

9.6. DESCRIPTION OF TRIAL INTERVENTION AND COMPARATOR

All of the hospitals involved in this trial are familiar with both techniques. All patients will receive analgesia at the discretion of the treating clinician as per local guidelines. In the absence of local guidelines, clinicians should adhere to the Royal College of Emergency Medicine best practice guidelines for the management of acute pain in children[31].

This trial will compare two surgical approaches to treat severe stable SCFE in children aged 8 - 15 years old inclusive.

9.7.1 Pinning In-Situ

This technique involves stabilisation of the femoral epiphysis in the current (i.e., non-anatomical) position with a minor procedure, accepting the inevitable deformity. The method used to stabilise the epiphysis will be at the discretion of the clinician. A record will be made of the operative details and the post-operative weight bearing status. In particular, details will be recorded if there is any concurrent surgical intervention used to improve the femoral shape (i.e., arthroscopic debridement). Any concurrent intervention must not seek to anatomically realign the physis.

9.7.2 Acute Correction

This technique seeks to acutely correct the position of the epiphysis at the site of the initial deformity (i.e., an intracapsular osteotomy to anatomically realign the physis) and thus restoring the normal anatomy. This procedure, if successful alleviates the need for further surgery and FAI. In this pragmatic trial the surgeon should follow the technique that is familiar to them as per their usual practice. A record will be made of the operative details, the post-operative weight bearing status and the nature of the physiotherapy employment in rehabilitation.

9.7.3 The Rehabilitation and Recovery Period

In this pragmatic trial, rehabilitation will be left to the discretion of the treating clinicians. However, a record of any rehabilitation input (type of input and number of additional appointments) together with a record of any other investigations/ interventions will be requested as part of the 8-week, 3, 6 and 12 and 24 month follow-up datasets from both patients and clinical teams.

9.7. BASELINE ASSESSMENTS

Baseline demographic data, a brief medical history and the PROMIS mobility instrument, Wong-Baker Faces Pain Scale and EQ-5D-Y health-related quality-of-life questionnaire will be collected.

9.8. CLINIC VISITS (AS PER STANDARD OF CARE)

Participants will usually attend orthopaedic follow-up regularly as part of standard care until skeletal maturity (approx. 16 years old), or at least for 2 years after the initial surgery to monitor for signs of avascular necrosis. No additional visits or procedures are required as part of the trial protocol at any follow-up time point.

After the participant has attended their early (usually 8 weeks post-intervention) clinical check-up, and subsequent (12 and 24 months) clinical check-ups, the local research team will perform a medical records check and complete the 'Site Follow-up' CRF. In addition, after the 24 months visit, the research team will transfer routinely collected images of the hip/pelvis that are collated within the PACS system. These will be transferred to the central trial office, where they will be assessed by an independent adjudication committee to quantify the degree of residual deformity. Details of standardised protocols and proformas used by the adjudication committee will be outlined in the data management plan. See Table 3 for specific data collection time points.

9.9. REMOTE FOLLOW-UP

At 8 weeks, 3, 6, 12 and 24 months post-randomisation, parents and/or participants will be contacted by the central trial team and invited to complete follow up questionnaires. These include the PROMIS, Wong-Baker, EQ-5D-Y, satisfaction with care, complications, educational participation and resource use questionnaires. See Table 4 for specific data collection time points.

9.10. SAMPLE HANDLING

No samples will be taken from participants for the purposes of this trial.

9.11. EARLY DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

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. Participant (or their parents) can withdraw by contacting the research team, with contact details 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 and safety analysis. The options for withdrawal will be explained clearly in the Patient Information Sheet. 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.

9.12. DEFINITION OF END OF TRIAL

The end of this trial is defined as the date all data queries have been resolved and the trial database is locked for analysis of the primary and secondary outcomes at 24 months.

10. SAFETY REPORTING

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 of the trial interventions are in common use. In light of this, we do not anticipate many serious adverse events (SAEs) associated with either treatment.

10.1. DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the 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.

10.2. REPORTING PROCEDURES FOR SERIOUS ADVERSE EVENTS

For the purpose of safety recording for this trial, only unexpected SAEs potentially related to the intervention will be reported immediately to the central trial team. When the local research team becomes aware of an SAE in a trial participant, the Principal Investigator (PI) will review the SAE locally and make a decision about the causality (i.e., likelihood of the event to be related/attributed to the intervention). Further details on grades of causality can be sought in the SAE reporting guidelines document available in the ‘Investigator Site File’. Following assessment of causality the PI will assess any related events for expectedness. For any SAEs assessed as unexpected and potentially related, the details of the event will

be entered on a SAE reporting form on the database, and the research team will notify the central trial team via email or telephone within 24 hours of the site trial team becoming aware of the event. Once received, causality and expectedness will be confirmed by the CI or delegate (Nominated Person). In the event that consensus is not reached between the PI and Nominated Person about assessment of causality and expectedness, this will be escalated to the CI for further discussion. However, if no consensus decision is reached about expectedness after further discussion within one working day, and the SAE is judged to be unexpected by any one of the PI, Nominated Person or CI, the event will be classified as an unexpected event.

An SAE should be reported to the REC that gave a favourable opinion to the Big BOSS study where in the opinion of the CI the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). All such events will also be reported to the TMG, TSC and the Data and Safety Monitoring Committee (DSMC) at their next meetings.

Adverse events that are unrelated to the injury, intervention or treatment will not be reported.

10.3. MANAGEMENT OF COMPLICATIONS

Foreseeable SAEs and adverse events not defined as serious that are related to the treatment of SCFE do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. The complications anticipated in the management of these patients (including readmission/ reoperation to address them) include:

- pressure sores,
- non-union of the bone,
- wound or bone infection,
- injury/irritation to nerves altering sensation to the lower limb or toes,
- implant irritation and the subsequent need to remove/adjust metal pin/screws (planned or unplanned),(i.e. screw cut out or backing out (metalwork displacement))
- heterotopic bone formation,
- hip dislocation,
- avascular necrosis,
- chondrolysis,
- reslip ((i.e., Recurrence of SCFE)),
- implant-related fracture

11. STATISTICS AND ANALYSIS

11.1. STATISTICAL ANALYSIS PLAN

A separate statistical analysis plan (SAP) with full details of all statistical analyses will be drafted early in the trial and finalised in advance of any inferential analysis of the data. The SAP will be written in accordance with the current OCTRU Standard Operating Procedures (SOPs) and will be finalised and agreed by the trial statistician, the CI and the TMG.

11.2. DESCRIPTION OF THE STATISTICAL METHODS

Results will be reported in accordance with the CONSORT Statement and relevant extensions [32, 33].

Standard descriptive statistics will be used to describe the demographics between the treatment groups. Binary and categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by means and standard deviations, or median and inter-quartile range if data are skewed.

The analysis of the primary and secondary outcomes will use the intention-to-treat principle, with all observable participants analysed in the group to which they were randomised to regardless of actual treatment received).

The PROMIS Mobility Score for Children at 24 months post-randomisation is the primary outcome of the trial. The primary analysis will use an analysis of covariance approach that adjusts for the baseline value and treatment group. This approach will have a greater power to detect the minimum important difference than the unpaired t-test which was used for the power calculation [34]. As recommended by ICH E9 [35], the model will also adjust for minimisation factors as fixed effects. An unadjusted analysis, that does not include minimisation factors, will also be performed.

Continuous secondary outcomes measured over time (PROMIS, Wong-Baker and EQ-5D-Y) will be compared using a mixed effects linear regression model. Models will include treatment, baseline score, time-by-treatment interaction and minimisation factors as fixed effects. Participants will be included as random effects. As satisfaction scores are expected to be non-normally distributed, this will be compared using unadjusted non-parametric methods (for example, Mann-Whitney or the Kruskal-Wallis test) for each timepoint separately. Educational participation will be analysed as total days missed during the 24-month follow up using Negative Binomial Dispersion regression model. The number and proportion of participants experiencing each type of complication will be summarised by treatment group.

11.3. SAMPLE SIZE DETERMINATION

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 standard deviation 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 Upper Extremity Score for Children are translated into standardised T-scores with a population mean of 50 and a standard deviation (SD) of 10. The minimum clinically important difference (MCID) of PROMIS paediatric measures is generally 3.0-5.0 [36,37].

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 major 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.[38]

11.4. DECISION POINTS

No interim analyses are planned. Interim analysis will only be conducted on the specific request of the DSMC. The oversight committees will review recruitment during the feasibility phase in order to make a recommendation regarding continued progress of the study against the specified stop/go criteria (see section 7).

11.5. THE 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.

11.6. PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA.

Missing data, for example due to withdrawal, protocol deviation or patient loss to follow-up, will be summarised and patterns analysed. Analysis of the primary and all secondary outcomes will be performed using available data. If there is sufficient or differential missing data, sensitivity analyses using multiple imputation techniques will be performed. These will explore the possibility of data being missing at random as well as departures from this assumption. All analyses of secondary outcomes will be performed using available data.

11.7. PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any proposed changes from the original SAP will be included in an updated protocol, updated SAP and/or reported in the final report as appropriate to the timing of the changes.

11.8. HEALTH ECONOMICS ANALYSIS

We will integrate an economic evaluation, informed by the NICE Reference Case [24] and reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[39]. The economic evaluation will be conducted from the perspective of the UK NHS and Personal Social Services. A Health Economics Analysis Plan (HEAP), providing full details of the prospective economic analysis, will be finalised before the end of follow-up.

Participants' use of primary, secondary and community care services, as well as medications will be collected using an electronic resource use questionnaire [40]. 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 [41, 42]. The primary economic outcome will be the incremental cost-effectiveness ratio (ICER) expressed as the incremental cost per QALY gained. Uncertainty in costs and QALYs will be assessed using bootstrap credible intervals, with the probability of cost-effectiveness at different

willingness to pay threshold values represented using cost-effectiveness acceptability curves. In the event that incremental costs and benefits are not convergent within the trial duration, 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.

12. DATA MANAGEMENT

The data management aspects of the trial are summarised here with details fully described in the Data Management Plan.

12.1. SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, patient-reported outcome measures that are submitted directly to the sponsor and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

12.2. ACCESS TO DATA

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor, the University of Oxford and the University of Liverpool for monitoring and/or audit of the trial. The data submitted by trial participants directly via the clinical database (i.e., electronic patient reported outcomes) will also be made available to the recruitment centre at which the participant was treated.

12.3. DATA RECORDING AND RECORD KEEPING

Participants' parents will be asked to provide their contact details as well as the contact details of an alternative friend or family member. Experience from numerous orthopaedic trauma trials has highlighted that collection of these additional data reduces loss to follow-up substantially. The secondary contacts will be automatically notified and they will be given the opportunity to give consent for us to hold their contact details or request that they are removed. If they have not responded within 14 days, their contact details will be automatically deleted. If the participant is 12 years or older and the parent has consented and child assented to the child being contacted, the participant's contact details will also be provided.

The case report forms will be designed by the trial manager in conjunction with the TMG. Data will be collected in electronic format with direct entry onto the trial database, including the collection of documentary evidence of consent and assent. Wherever possible, trial data will be entered directly by site staff or participants/parents. 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. We will use an electronic trial platform that 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. REDCap (Research Electronic Data Capture) is the planned platform. All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent/assent forms, will be held on a server located in an access controlled server room at the University of Oxford. The data will be accessible only to members of the research team based on their role within the trial. 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 transferred and who has access to it along with a fair processing statement will be available for the public to see on the trial website.

Any paper forms, if collected, with participant/parent-identifiable information will be held in secure, locked filing cabinets within a restricted area. The identifiable data will be kept separately from the outcome data obtained from/about the participants (both paper and electronic). Participants will be identified by a trial ID only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required.

The trial will be reported in line with the CONSORT statement[32] and the appropriate extensions including non-pharmacological and patient reported outcomes[33,34].

Please see Table 5 for data retention periods.

Table 5 Data retention periods

Data/Document		Retention Period	Retention Location
Contact Details		12 months after completion of the trial	University of Oxford
Big BOSS Study Parent Consent and Child Assent forms	Investigator Site File copy	12 months after the youngest participant reaches 21 years of age	Recruitment centre
	Medical Record copy	As per local hospital policy	Recruitment centre
	Central Trial Team copy	12 months after completion of the trial	University of Oxford
Big BOSS Study Participant Consent forms (if applicable)	Central Trial Team copy	12 months after the youngest participant reaches 21 years of age	University of Oxford
Research Data	De-identified	Five years after publication of the primary results	University of Oxford
	Anonymised	Indefinitely	University of Oxford

Big BOSS Information Study Consent forms	Qualitative Trial Team copy	12 months after the youngest participant reaches 21 years of age	University of Liverpool
Big BOSS Information Study Informed Consent Discussion Transcriptions	De-identified	10 years after publication of the primary results	University of Liverpool
Big BOSS Information Study Interview Transcriptions	De-identified	10 years after publication of the primary results	University of Liverpool

13. QUALITY ASSURANCE PROCEDURES

This trial will be overseen by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. A rigorous programme of quality control will be implemented to ensure compliance to the current approved protocol, GCP, relevant regulations and OCTRU SOPs. Quality assurance checks will be undertaken by the Trial Management Team to ensure integrity of randomisation, trial entry procedures and data collection. Inspections of the Trial Master File will be carried out by the OCTRU Quality Assurance team (at least once in the lifetime of the trial, more if deemed necessary). Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored centrally.

Additionally, the trial may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. RISK ASSESSMENT

A risk assessment and monitoring plan will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. TRIAL MONITORING

The monitoring activities will be based on the outcome of the risk assessment. Quality control procedures will be undertaken during the recruitment and data collection phases of the trial to ensure research is conducted, generated, recorded and reported in compliance with the protocol, GCP and ethics committee recommendations. The CI and the Clinical Trial Manager will develop data management and monitoring plans.

13.3. TRIAL COMMITTEES

13.3.1 Trial Management Group

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager at the Oxford Trauma and Emergency Care group (University of Oxford). This will be overseen by the TMG, who will meet monthly to assess progress. A PPI representative will be an integral member of the TMG. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres.

The trial statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

13.3.2 Trial Steering Committee

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the NIHR and will be drawn up in a TSC charter which will outline its roles and responsibilities. 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 trial 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 trial

The TSC will include at least one PPI representative as an independent member.

13.3.3 Data and Safety Monitoring Committee

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial. The trial DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to review any formal interim analyses of effectiveness. They will, however, review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety (see section 10.2 for details). DSMC meetings will be held at least annually during the recruitment phase of the trial. Full details including names will be included in the DSMC charter.

14. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g., consent process or administration of trial intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

15. 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 trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the

Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days).

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. DECLARATION OF HELSINKI

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

16.2. GUIDELINES FOR GOOD CLINICAL PRACTICE

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. APPROVALS

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any other participant-facing material will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. OTHER ETHICAL CONSIDERATIONS

The two interventions used in this trial are both standard clinical practice and currently offered to patients across the UK. Surgeons therefore have community equipoise.

We are aware that being part of a trial, particularly a trial involving randomisation, may be a concern for some parents. The research team members at the recruitment centres all have extensive experience in working with children and parents, and the patient materials have been optimised through patient engagement. The *Big BOSS Information Study* will further ensure that patients are engaged in the consent process and will identify any concerns from families that can be shared across the team of investigators.

Recompense for data costs caused considerable debate amongst our PPI forum (through the NIHR Young Persons Advisory Group and Parents Advisory Group). 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 trial.

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), parents advisory group (PAG), health care professional, our PPI co-investigators and our PPI advisory team. 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). To supplement the

traditional online 'Patient Information Sheet' content, parents and children from our previous children's trauma trials (FORCE IRAS 246654, CRAFFT IRAS 264593 and SCIENCE IRAS 259931), have identified that a simplified information leaflet is more useful to frame a conversation around consent. Parent co-applicants and members of the PAG have identified the key information that they wish to have available in this simplified document.

16.5. REPORTING

. This protocol will comply with all current applicable REC, host organisation, Sponsor and funder reporting requirements. In addition, an End of Trial notification and final report will be submitted to the applicable parties.

16.6. TRANSPARENCY IN RESEARCH

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database, 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.

16.7. PARTICIPANT CONFIDENTIALITY

The trial will comply with the General Data Protection Regulation (GDPR) and UK Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant trial number on all trial documents, any electronic database(s) and extracts. With the exception of DOB, all identifiable data will be held in a separate trial database project, DOB will be used during the randomisation process to ensure participant uniqueness. The authorisation functionality within the data collection system will be utilised to ensure that identifiable data can only be accessed by appropriate members of the trial team with a demonstrated need and only used to communicate with the participant (e.g. sending follow-up reminders for online form completion or telephone follow-up). All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data. Full details will be recorded in the Data Management Plan.

16.8. EXPENSES AND BENEFITS

A £10 gift voucher will be offered for participation in the research project. These funds are offered to compensate for any cost and inconvenience participant families may have incurred by using their mobile phone or computer to complete the outcome measure assessments.

A £20 gift voucher will be offered to parents and/or young people who complete an interview for the *Big Boss Information Study* to compensate them for their time.

17. FINANCE AND INSURANCE

17.1. FUNDING

This trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (NIHR131176). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

17.2. 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.

17.3. CONTRACTUAL ARRANGEMENTS

Alder Hey Children's NHS Foundation Trust acts as the contractor for this project for the National Institute for Health and Care Research. Appropriate contractual arrangements will be put in place between collaborators and all other third parties. An Organisation Information Document will be used as an agreement between Sponsor (Alder Hey Children's NHS Foundation Trust) and participating NHS Organisations.

18. PUBLICATION POLICY

The trial monograph will be prepared by the TMG when the primary end point is completed (two year follow up). No patient identifiable information will be contained in any form of dissemination of trial results.

Dissemination will be via traditional and novel methods:

- Conference: Traditional conference dissemination will focus on presentations to include the key professional stakeholders (emergency medicine doctors, orthopaedic emergency nurse practitioners and trainees in emergency medicine and orthopaedics).
- Publications: Key outputs will be published in high-impact journals with publicity sought in other professional journals (e.g. Pulse, HSJ, Nursing Times, popular media). We will ensure that plain English summaries are published alongside the full paper, along with links to other digital media on the trial website to explain the trial result in an accessible format – i.e. an explainer animation and infographic. Given the frequency of the injury, this is also likely to be of interest to international press-outlets.
- Policy makers: We will ensure the development of links with key organisations such as NICE, NHS Information Centre, NHS England and Quality Observatories to contribute to and capitalise on their networks. Most importantly the outputs will directly contribute to the NICE SCFE guidelines [IPG511][12].
- 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". Finally, we update the Wikipedia page for SCFE and include details of the trial result.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

20. ARCHIVING

Documents will be archived as per the appropriate standard operating procedures as prepared by the Oxford Clinical Trials Research Unit.

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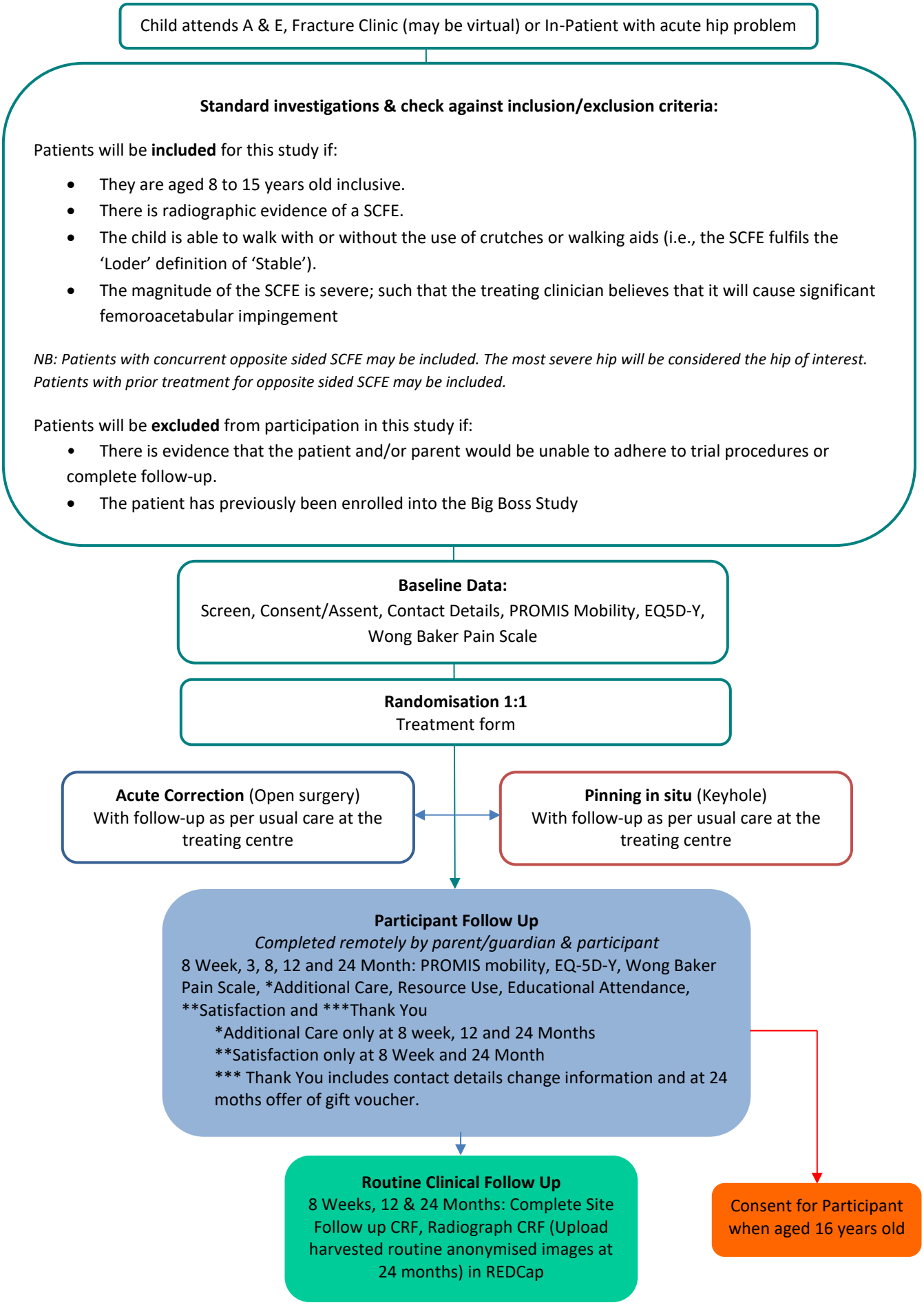
22. APPENDIX A: BIG BOSS STUDY FLOW CHART



23. APPENDIX B: DATA COLLECTION

The data to be collected on case report forms from participants and/or their parent/guardian and site staff is listed below:

Screening data: (*Completed at hospital by local study team member and collected from all screened patients)*

- Date of diagnosis and screening
- Sex
- Age on day of screening
- Ethnicity
- Index of Multiple Deprivation Score
- Side of hip problem
- Current/previous opposite sided SCFE
- Height/Weight
- Eligibility criteria
- Willingness to participate
- Treatment preference (if decline participation)

Contact details: (*Completed at hospital by local study team member)*

- Child Name
- Child NHS/CHI/H&C Number
- Child DOB
- Parent/Guardian Name
- Secondary Contact Name
- Email address
- Mobile Phone number
- Preferred method of contact
- House Number and Postcode

Baseline data: *(Completed at hospital by local study team member with participant)*

- PROMIS Mobility
- EQ-5D-Y
- Wong Baker Faced pain scale

Randomisation form: (*Completed at hospital by local study team member)*

- Participant identifiers: DOB, Sex and Site
- Stratification: Current/previous opposite sided SCFE (presence/absence) and age group (8-10 years or 11-15)
- Consent Confirmation

Baseline Treatment form: *(Completed at hospital by local study team member). Window for completion: + 4 weeks (28 days)*

- Treatment allocation and was it received
- Operation details
- Date of Operation
- Date of Admission/Discharge
- Grade of surgeon
- Intraoperative problems

- Post Intervention instructions (weight bearing status)

Participant Follow Up at Week 8, 3, 6, 12 and 24 Months: *(Completed remotely by parent/guardian and participant). Window for completion: Week 8 + 3 weeks (21 days), 3 month + 6 weeks (42 days), 6 Month +12 weeks (84 days). 12 & 24 Month + 3 months (90 days)*

- PROMIS mobility
- EQ-5D-Y
- Wong Baker Pain Scale
- Additional Care (complications, additional surgery)
- Resource Use (additional costs, hospital and other care, medications, appliances)
- Educational Participation
- Satisfaction (only at 6 Week and 24 Month)
- Thank You (Thank You includes contact details change information and at 24 moths offer of gift voucher)

Routine Clinical Follow Up at Week 8, 12 & 24 Months: *(Completed at hospital by local study team member) Window for completion: Week 8 + 4 weeks (28 days), 12 & 24 Month + 3 months (90 days)*

- Site Follow up CRF (complications and additional surgery)
- Radiograph CRF (Upload harvested routine anonymised images)

Ad Hoc CRFs: *(Completed at hospital by local study team member and/or central study team)*

- Protocol Deviation
- Serious Adverse Event
- Withdrawal
- Transfer

24. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
AM002	2.0	16Oct2023	Louise Spoors	Correction of minor typographical errors. Addition of wording to include "University of Liverpool", who act as joint data controller for the study in section "12.2 Access to Data" as this was previously omitted in error. Addition of wording "and children" to section "9.3.1 Consent for Data Linkage with the Non-Arthroplasty Hip

				Registry" as this was previously omitted in error.
AM 004	3.0	21Aug2024	Louise Spoors Daniel Perry Jennifer Kirton	Section 7: Addition of "Progression Criteria". Section 7 and 9.2.1: Changes to BigBOSS Information Study to include interviews with sites not partaking in the study and/or those sites who have not screened participants for the study.

List details of all protocol amendments here whenever a new version of the protocol is produced.
Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).