CRAFFT – Children's Radius Acute Fracture Fixation Trial

A multi-centre prospective randomised non-inferiority trial of surgical reduction versus non-surgical casting for displaced distal radius fractures in children

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We 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?

The most common part of the body for a child to break is their wrist. Most need just a plaster cast, but some have surgery to reset the bones before they go in a plaster cast. These operations are really common but doctors are unsure whether they are really necessary in younger children. In younger children up to 10 years old even when the bones break and move totally out of place, there is evidence to suggest that the wrist will heal well and will grow back to a normal shape over a few months. However, families and some doctors worry that if the bones aren't reset early, then the wrist might not fully return to normal (may still look bent) and it will take a long time to get back to normal activities. On the other hand, there are risks with resetting bones, including that the child will need an anaesthetic or sedation, they may get scars, and may get an infection. Parents and children want to know if surgery is really necessary, or whether a plaster cast with natural healing will be as good.

What is the question being asked?

When children up to 11 years old break their wrists, do they need surgery to reset the bones, or will nature 'self-correct' the bones as they heal without restricting the use of the arm?

What sort of study is it?

This study is called a trial, which is the best way to compare treatments to get a proper answer. In the Children's Radius Acute Fracture Fixation Trial (CRAFFT), 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. Parents and children won't be able to choose which treatment they get. To make things fair, this will be decided using the technique of randomisation by a computer.

How many children will be involved?

We plan to include at least 750 children over a two-year period from more than 32 hospitals. This participant number is calculated based on previous scientific research to ensure that the study is large enough to reach a firm conclusion. We will ensure we continue the study until we have included at least 200 patients who have a 'completely off-ended' fracture (i.e. the most severe fractures).

What will families be asked?

Children aged 4-10 years old with a broken wrist might be asked to join the study. Only those with more severe breaks where surgery is being considered will be included. Families who agree to join the study will be split fairly into two groups:

1. SURGERY – the children will have an anaesthetic or be sedated so their bones can be reset in theatre, and a plaster cast put on their wrist. Sometimes, if the doctor thinks it necessary, a small cut will be made and a wire or a plate and screws will be inserted to hold the broken bones in position.

2. NON-SURGICAL CASTING - a plaster cast will hold the bones in position, but the bones will not be reset and they will be allowed to heal naturally.

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

All children will be followed up for 3 years. The study will ask about the use of the arm, pain, how the arm looks, any complications and the number of hospital visits.

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. Phoebe, Philippa and Evan (two parents and a teenager) 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?

This question began at an 'NIHR Trauma Workshop' in 2017. Evan (12 years old) was the only child representative at this event with over 100 surgeons. Two years ago Evan had a serious bike accident needing surgery, but is now riding his bike again! Evan and his mum Philippa helped develop this question, and are keen to be involved throughout the study.

This research question has been discussed with the NIHR Young Person's Advisory Group, and the Parents Advisory Group (PAG) in Liverpool, and outcomes for the study were determined at an event held with families at Chester Zoo. Parents felt that their initial fears about not having surgery were overcome by showing them pictures of how well the bones heal and straighten over time. In fact, parents identified that they would only want surgery if it is better than not having surgery. A parent from the PAG, Phoebe Gibson, is also part of the team doing this study.

3. SYNOPSIS

Study Title	Children's Radius Acute Fracture Fixation Trial		
Acronym	CRAFFT		
Study Registration	The study has been registered with the current controlled trials database under reference number ISRCTN10931294 NIHR CRN Portfolio: 44878		
Sponsor	University of Oxford		
Funder	National Institute for Health Research (NIHR)		
Study Design	Multi-centre prospective randomised non-inferiority trial		
Study Participants	Children 4 to 10 years old inclusive with evidence of a severely displaced radius fracture.		
Planned Sample Size	A minimum of 750 patients, to ensure there are at least 200 patients with a 'completely off-ended' fracture.		
Planned Study Period	01/12/19 – 30/10/23		
Planned Recruitment Period	01/04/20 – 30/04/22		
	Objectives	*Outcome Measures*	*Time Point*
Primary	To determine whether non-surgical casting is non-inferior to surgical reduction, measured using observed differences in the PROMIS Upper Extremity Score at three months post-treatment.	PROMIS UE	3 months
Secondary	1. To quantify and draw inferences from differences in function using the PROMIS Upper Extremity Score between non-surgical casting and surgical reduction during the first year post-treatment.	PROMIS UE	Baseline, 6 weeks, 3, 6 and 12 months
	2. To quantify and draw inferences from observed differences in pain scores between non-surgical casting and surgical reduction during the first year post-treatment.	Wong-Baker Faces Pain Score	Baseline, 6 weeks, 3, 6 and 12 months
	3. To quantify and draw inferences from observed differences in quality of life using EQ-5D-Y between the trial treatment groups during the first year post-treatment.	EQ-5DY	Baseline, 6 weeks, 3, 6 and 12 months
	4. To determine the complication rate up to 1-year post-treatment, including re-fracture, the need for further	Complications	Removal of the cast (clinical), 6

	operative fixation and the absence of radiographic remodelling.		weeks, 3, 6 and 12 months
	5. To estimate the cost-effectiveness of the treatments to the NHS and the broader economy, up to 1-year post-treatment.	Healthcare Resource use	6 weeks, 3, 6 and 12 months
	6. To quantify and draw inferences from parental satisfaction with the cosmetic appearance of the arm between non-surgical casting and surgical reduction during the first year post-treatment.	VAS Cosmesis	6 weeks, 3, 6 and 12 months
	7. To quantify and draw inferences from patient satisfaction between non-surgical casting and surgical reduction during the first year post-treatment.	Satisfaction score	12 months
	8. To determine the impact of injury, treatment and recovery on parent and child experience of daily life and the outcomes that are important to them.	Child and parent experiences	3 and 12 months
	9. To determine the barriers and facilitators to trial recruitment from parent/child and staff perspectives.	Child, parent and staff experiences	Pilot phase
	Long-term outcomes. To be reported separately. 10. To quantify and draw inferences from longer-term pain, function & complications annually up until 3 years post-treatment.	PROMIS Wong-Baker Faces Pain Score EQ-5DY VAS Cosmesis Complications	Annually (2 and 3 years)
Intervention	Non-surgical casting		
Comparator	Surgical reduction		

4. ABBREVIATIONS

AUC	Area Under The Curve
BNF	British National Formulary
BOSS	British Orthopaedic Surgery Surveillance
BSCOS	British Society Of Children's Orthopaedic Surgery
CAT	Computer Adaptive Test
CI	Chief Investigator
CRAFFT	Children's Radius Acute Fracture Fixation Trial
CRF	Case Report Form
DASH	Disabilities Of The Arm Shoulder And Hand Score
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-To-Treat
MCID	Minimally Clinically Important Difference
NHS	National Health Service
NIHR	National Institute For Health Research
OCTRU	Oxford Clinical Trials Research Unit
ONS	Office for National Statistics
OTS	Orthopaedic Trauma Society
PACS	Picture Archiving and Communication System
PAG	Parents Advisory Group
PERUKI	Paediatric Emergency Research In The UK And Ireland
PI	Principal Investigator
PODCI	Pediatric Outcomes Data Collection Instrument
PPI	Personal And Public Involvement
PROMIS	Patient Report Outcomes Measurement Information System
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SAP	Statistical Analysis Plan
TSC	Trial Steering Committee
UE	Upper Extremity
VAS	Visual Analogue Scale
YPAG	Young Persons Advisory Group

5. BACKGROUND AND RATIONALE

Fractures of the wrist (distal radius and ulna) are the most common fractures in children,[1] and constitute around half of childhood long bone fractures seen in emergency departments. Most are relatively minor, with some not requiring any treatment and others just a simple plaster cast or splint. Operative intervention is currently the mainstay of treatment for more serious (displaced) distal radius fractures in the UK. Such patients undergo realignment of the bones, a procedure usually performed in the operating theatre under general anaesthesia. During the procedure, the normal anatomy is restored immediately by external manipulation, which may be followed by the insertion of metal pins or plates, after which it is held securely in a plaster cast. This surgical treatment carries the risks and costs associated with admission and anaesthesia, and complications related to the surgery. Metal pins are most commonly used to hold the bone, but these result in complications in around a third of cases,[2,3] which include infection, injuries to surrounding nerves and further surgery (approx. 7%). The use of pins and plates also necessitate later procedures to remove these implants.

Whilst operative treatment is the mainstay of treatment for displaced fractures, it is widely recognised that this may not always be necessary. Children's bones are fundamentally different to adult bones; principally because the bones of children are still growing. Growth of the bone arises from specific regions at the ends of a bone, called the physis or 'growth plate'. As well as enabling growth, the physis also enables a process called 'remodelling' to rapidly occur[4]. Remodelling allows deformity caused by fractures at or near the physis to self-correct as the bone grows – with the correction of angulation, length and translation (overlap) of a fracture possible. There is a growth plate (physis) next to the wrist of children where longitudinal growth of the bone originates. Fractures commonly occur either at the level of the physis of the radius (called a 'physeal fracture' or 'Salter-Harris fracture') or adjacent to the physis (called a metaphyseal fracture).

Studies as early as 1935 showed that fractures near the physis of the wrist tend to remodel without any manipulation, and that the wrist has huge potential for remodelling in children.[5] The rate of remodelling at the wrist is exponential, with the most marked remodelling in the early months following a fracture and little or no improvement seen beyond 3 years.[6] Remodelling occurs most markedly in children with the most remaining growth, with studies consistently demonstrating good results amongst children up to 11-years-old[6,7]. A study of eighty-five wrist fractures through the physis amongst a group of children aged up to 10 years demonstrated that all deformities completely remodelled almost irrespective of the degree of displacement and that no child had any subjective or objective loss in arm function[8]. Fractures adjacent to the physis (metaphysis) have similarly good outcomes. Even the most severe metaphysis fractures (in which the bones are broken such that the fracture ends overlapped, known as 'completely off-ended' fractures), remodelled in children up to 11-years-old, with no residual functional impairment for the child[9,10]. Most recently, at the 2018 Pediatric Orthopaedic Association of North America Meeting a randomised trial of surgery vs. no-surgery for off-ended metaphyseal fractures demonstrated no difference between interventions, although this was a small poor quality trial without patient reported outcomes.[11]

There is an abundance of evidence showing the innate ability of young children's bones to remodel without the need for manipulation, which makes non-surgical treatment standard in many parts of the world[12]. However, UK practice is almost universally in favour of surgically correcting displaced wrist fractures irrespective of the age of the child. This trend is partly attributable to the influence of two prominent UK surgeons in the 1990s who believed that these fractures should be manipulated and fixed with wires.[13,14]

UK practice is now more interventional than the US, with only one centre routinely offering non-operative care to families. Surgeons find it challenging to manage the uncertainty required in waiting for these fractures to remodel, with unease about whether the bone will truly correct itself, and uncertainty about how families will react to waiting for the initial bent appearance of the child's arm to improve.[9] There is little evidence to guide decision-making, and the available studies are typically low quality retrospective case series with unstructured follow-up and poorly collected functional outcomes.

Doctors, both within the UK and internationally, now feel compelled to strengthen this evidence base and determine whether these fractures really require surgery. This question was prioritised by the NIHR following a trauma prioritisation event involving surgeons and patients at the Royal College of Surgeons of England. Furthermore, we recently led a priority setting exercise on behalf of the British Society of Children's Orthopaedic Surgery (BSCOS), which also identified this to be one of the 'top five' research priorities in children's trauma.[15] Internationally, the IMPACCT Collaborative (North America & Europe) has also highlighted this as one of their four key questions in children's trauma.

5.1. Current practice

Hospital Episode Statistics (HES) from England [unpublished] reveal that in 2015/16 2,500 children below 10-years old were admitted for surgery to realign the bones of the wrist following injury every year. This number is corroborated by audits at three NHS trusts, which were undertaken to quantify the number of eligible participants for this study. Alder Hey Hospital identified 48 patients up to 11-years-old within a 1-year period (14 (30%) were completely off-ended). All underwent manipulation and 18 also underwent wire or plate fixation. Five (28%) of those treated with wires or plates developed complications. At Bristol and Sheffield Children's Hospital the numbers over one year were similar, with 43 and 42 children respectively. Of those from Bristol and Sheffield, 30 (35%) were completely off-ended, and 30 (35%) underwent wire or plate fixation.

5.2. Why is this important?

These fractures represent a high-volume childhood injury – based on HES data, in England alone this injury would almost fill two operating theatres running at full capacity every day of the year. Given the costs of admission and surgery, NHS Digital estimates the annual secondary care costs for these injuries amongst children up to 10-years-old (related to the admission alone for those 2,500 cases submitted to HES) is around £4m. Furthermore, HES data is likely to be a considerable underestimate as many hospitals do not submit day-case admissions to HES, and some hospitals may perform such procedures under sedation, which is a resource-intense procedure in the Emergency Departments.

By clearly determining whether non-surgical casting is non-inferior to surgical fixation, we could also avoid the risks for children of undergoing surgery and reduce the burden on trauma operating theatre capacity; particularly in the 'peak' childhood fracture season during summer months.[16]

6. OBJECTIVES AND OUTCOME MEASURES

The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost-effectiveness of non-surgical casting, compared to surgical reduction for the treatment of severely displaced fractures of the distal radius in children.

Table 1: Objectives and Outcome Measures

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure
Primary Objective To determine whether non-surgical casting is non-inferior to surgical reduction, measured using observed differences in the PROMIS Upper Extremity Score at three months post-treatment	PROMIS Upper Extremity	3 months
Secondary Objectives 1. To quantify and draw inferences from differences in function using the PROMIS Upper Extremity Score between non-surgical casting and surgical reduction during the first year post-treatment.	PROMIS Upper Extremity	Baseline, 6 weeks, 6 and 12 months
2. To quantify and draw inferences from observed differences in pain scores between non-surgical casting and surgical reduction during the first year post-treatment.	Wong-Baker Faces Pain Score	Baseline, 6 weeks, 3, 6 and 12 months
3. To quantify and draw inferences from observed differences in quality of life using EQ-5D-Y between the trial treatment groups during the first year post-treatment	EQ-5DY	Baseline, 6 weeks, 3, 6 and 12 months
4. To determine the complication rate up to 1-year post-treatment, including re-fracture, the need for further operative fixation and the absence of radiographic remodelling	Complications	Removal of the cast (clinical), 6 weeks, 3, 6 and 12 months
5. To estimate the cost-effectiveness of the treatments to the NHS and the broader economy, up to 1-year post-treatment	Healthcare Resource use	6 weeks, 3, 6 and 12 months

6. To quantify and draw inferences from parental satisfaction with the cosmetic appearance of the arm between non-surgical casting and surgical reduction during the first year post-treatment.	VAS Cosmesis	6 weeks, 3, 6 and 12 months
7. To quantify and draw inferences from patient satisfaction between non-surgical casting and surgical reduction during the first year post-treatment.	Satisfaction Score	12 months
8. To determine the impact of injury, treatment and recovery on parent and child experience of daily life and the outcomes that are important to them	Child, parent / guardian and staff experiences	Throughout study
9. To determine the barriers and facilitators to trial recruitment from parent/child and staff perspectives	Child, parent / guardian and staff experiences	Pilot phase
Long-term outcomes. To be reported separately 10. To quantify and draw inferences from longer-term pain, function & complications annually up until 3 years post-treatment.	PROMIS Wong-Baker Faces Pain Score EQ-5DY VAS Cosmesis Complications	Annually (2 and 3 years)

6.1. Outcome measures

We have explored potential outcomes with the parents and children who advise our research. Children believe that early return to normal function is most important to them, therefore the function at 3 months was chosen to be the primary outcome. Given the age of participants all outcomes will be proxy-reported by the parents, with the exception of pain, which will be child-reported. A schedule outlining the timelines for data collection can be found in Table 1.

Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children.

This is a well-validated assessment of upper extremity function in children, encompassing both activities of daily living, participation in school activities and hobbies. This outcome is used in other studies funded by the NIHR-HTA programme including SCIENCE (17/18/02) and FORCE (17/23/02).

In general, 'PROMIS scores' are a collection of patient-reported health status tools available for children and adults that were developed to be disease non-specific in collaboration with the US National Institute for Health. 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 for upper-extremity function. PROMIS is available in full (30 questions), short-form (8 questions) 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 participant could answer a distinct set of questions to arrive at their score. This CAT version will be used in this trial.

The PROMIS Upper Extremity Score for Children has been demonstrated to have convergent validity with other tests used in the assessment of upper limb function in children with congenital limb abnormalities, [17] Disabilities of the Arm Shoulder and Hand Score (DASH r=0.80 p<0.001), and Pediatric Outcomes Data Collection Instrument (PODCI r=0.70 p<0.001). DASH[18] is an adult measure of upper limb function with items that lack face validity amongst children (NB: DASH S/PA Module is distinct from the general DASH outcome tool), and PODCI is a general measure of disability.[19] The PROMIS Upper Extremity Score for Children correlates better to physiological tests of upper limb function (grip strength and pinch strength r>0.6 p<0.05),[17] than these other patient-reported measures. In the congenital limb population, the PROMIS-CAT test was also the only tool without ceiling effects. Further evidence of the absence of ceiling effects for the PROMIS Upper Extremity Tool, and concordance with 'legacy Upper Limb PROMs', was recently presented at the meeting of the American Academic of Orthopaedic Surgeons.[20]

Although PROMIS enables a self-reported function from 8-years-old, and proxy-reported prior to this, in this trial the parent-reported function amongst all age groups of children will be used. This is in line with advice that we have received from PROMIS developers to use a single version of the tool wherever possible.

Wong-Baker FACES Pain Scale[21]

The Wong-Baker faces pain score is a validated self-reported tool that will be self-reported amongst all children in the study. It is an ordinal assessment of pain outcomes, using a series of six facial-expressions to illustrate the degree of pain intensity. A numerical rating is assigned to each face (from 0 - 'no hurt' to 10 – 'hurts worst'). It has been validated for use amongst children over 3-years-old, including in the Emergency Department setting. It is particularly useful amongst younger children, as only one third of children 5-14 years understand the concept of a visual analogue scale

EQ-5D-Y[22]

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 proxy-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 CRAFFT trial 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 but particular note will be made of complications related to the cast (including, but not limited to, pressure areas) or surgery (including, but not limited to wound infection,

nerve injury, scar problems (overgranulation/hypertrophy/keloid)), and the need for further unplanned surgery in either group (including surgery for revision, re-fracture or broken metalwork). Planned surgery for the removal metal pins/screws/ plates will be recorded as part of routine treatment, and will not be regarded as a complication.

Any digital images of the wrist that have been collected as part of routine practice will be harvested from PACS at one-year post-treatment. A further harvest of routinely taken images during the long-term follow-up will be collected at 3 years post-treatment. No specific imaging is required at any stage for research purposes. Where available, the images will be used to assess the degree of residual deformity. The collection of routine digital images will constitute standard care under the definition provided by the Radiation Assurance carried out by the Health Research Authority (HRA).

Cost effectiveness

Resource use and quality-of-life data will be collected prospectively over the first year of patient follow-up. A UK NHS and Personal Social Services (PSS) perspective will inform the primary analysis. A broader social perspective will include out-of-pocket expenses, parental absence from work and any periods of school absence. Details are provided in 9.2.

Parent assessment of cosmesis & parent satisfaction with care

Arm appearance may be a concern to parents and surgeons. In the non-operative group, the arm will initially appear bent and straighten with growth. The perception of cosmesis will be collected using a Visual Analogue Scale in both the operative and non-operative groups. Also parents of children in either intervention group will be assessing their level of satisfaction with the treatment received.

7. STUDY DESIGN

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

7.1. Summary of research

The proposed project is a two-phased study. Phase 1 (internal pilot) will confirm the expected rate of recruitment and test data collection procedures in a large-scale multi-centre randomised controlled trial. Phase 2 (main RCT) will take place in a minimum of 32 UK centres.

7.1.1 Internal Pilot Summary

The pilot will take place at a minimum of 15 centres over 9 months. The aims of the internal pilot will be threefold: (1) We will determine the number of eligible and recruited patients in the centres. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent or withdraw, will be recorded. (2) We will use this initial period to optimise the electronic data collection procedures. (3) An integrated qualitative study will be undertaken to explore the acceptability of the proposed interventions and enhance study procedures to healthcare professionals, patients, and their parents.

Stop/go criteria with regards to progression to the main phase will be based on a recruitment target for the pilot of 125 patients. The Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will closely monitor recruitment in addition to the funding body. If the trial is stopped, all trial patients will be followed up per protocol. It is intended that the trial will progress seamlessly into the main phase, with internal pilot patients included in the final analysis.

7.1.2 Main Trial Summary

The main trial will recruit from a minimum of 32 centres across the UK. It is expected that recruitment in the main phase will take a further 16 months to reach a minimum of 750 patients; ensuring there are at least 200 patients with a 'completely off-ended' fracture.

7.1.3 Trial Structure

All children aged 4-10 years inclusive presenting to the trial centres with a displaced fracture of the distal radius are potentially eligible to take part. Upon presentation, children will receive analgesia and will be temporarily immobilised for comfort as per the usual practice of the treating centre. In many hospitals the decision related to definitive treatment is taken in the emergency department; in others the child may be discharged to an early appointment in the fracture clinic (usually the following day). 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 consent/assent has been gained, local research-trained staff will collect baseline demographic data, function using the Patient Report Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children, pain-intensity using the Wong-Baker FACES Pain Scale and health-related quality of life using the EQ-5DY.

Randomisation by minimisation with stratification factors: centre, fracture type at presentation (completely off-ended or incompletely off-ended), fracture location (metaphyseal or physeal) and age group (4-6 years or 7-10 years) will be provided online by the Oxford Clinical Trials Research Unit (OCTRU). Each patient will be randomly allocated (1:1) to either casting or surgical reduction. After treatment, patients will be asked to complete further questionnaires on function, pain, quality of life, cosmesis and satisfaction at 6 weeks, 3 months, 6 months and 12 months after treatment. Data will be collected primarily electronically (telephone interview where required) with email and/or text message prompts.

After completion of the main phase of the study, patients will be followed-up for an additional two years. Three years is known to be the period over which the bone can continue to change shape (remodel) and can therefore affect the outcomes. At 2 and 3 years post-treatment we will assess function, pain, quality of life and cosmesis.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Children between 4 and 10 years of age with evidence of a severely displaced radius fracture will be recruited.

8.2. Inclusion Criteria

Patients will be included for this study if:

- Male and Female children aged 4 to 10 years inclusive.
- Parents/guardians willing and able to give informed consent for their child's participation in the study
- There is radiographic evidence of a severely displaced wrist fracture at or adjacent to the physis (Salter-Harris II or a metaphyseal fracture); with or without a corresponding ulna fracture.
- The treating clinician believes that they may benefit from surgical reduction with or without fixation.

8.3. Exclusion Criteria

Patients will be excluded from participation in this study if:

- The injury is more than 7 days old.
- The injury is part of a more complex wrist fracture (i.e. open or fracture extending into the joint).
- There are other fractured bones elsewhere in the body, in addition to the affected wrist injury.
- There is evidence that the patient and/or parent would be unable to adhere to trial procedures or complete follow-up, such as insufficient English language comprehension, developmental delay or a developmental abnormality or no access by parents to mobile data/internet.

9. PROTOCOL PROCEDURES

9.1. Data Collection

Baseline data and complication data will be completed during the primary and routine follow-up clinical appointment (at 6-8 weeks) by recruiting team. Thereafter, an advance notification will be sent when questionnaires are due and then parents will be prompted to complete questionnaires at 6 weeks, 3 months, 6 months, 1-year and annually until 3 years post-treatment. All questionnaires will be proxy-reported by the parent, with the exception of the Wong-Baker pain score. A direct link to the on-line questionnaire will be sent via a text message and/or email when the questionnaire is due. Further reminder emails and text messages will be sent if the required data are not provided. If the parent has not responded to the initial and reminder messages within a specified timeframe (the time allowed will vary for each of the time points), or if the central trial team have queries relating to data that has been entered by the parent/guardian and it is not appropriate for the site to answer these, we will attempt to contact the parent/guardian to obtain (or request clarification of) the outcome data over the telephone or by email/text. Exact timelines of reminders and frequency of phone calls will be specified in the data management plan for this trial. If the parent cannot be contacted, we may contact the participant's secondary contact (if these details are available). To determine if and when parents/participants are opening the reminder e-mails we will use technology to track the e-mail, which encompasses a single pixel embedded within the body of message.

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, recruitment centres will be prompted to complete this form to give full details of the event.

Once the final questionnaire is completed at the end of year one, a £10 gift voucher will be offered to the parent as compensation for any costs (i.e. mobile phone data) incurred whilst completing the outcome measure assessments.

Long-term outcomes

The rate of remodelling at the wrist is exponential, with the most marked remodelling in the early months following a fracture and little or no improvement seen beyond 3 years. We will therefore contact the patients on an annual basis by text message to collect updated PROMIS, Wong Baker Pain Score, EQ-5DY, VAS cosmesis and complications until 3 years post-treatment. This will be reported separately.

TIME POINT	DATA COLLECTION
Pre-treatment (clinic)	PROMIS UE baseline, Wong-Baker, EQ-5D-Y
Removal of immobilisation (clinic)	Complications
6 weeks	PROMIS UE, Wong-Baker, EQ-5D-Y, VAS Cosmesis, complications and economics questionnaire
3 months	PROMIS UE, Wong-Baker, EQ-5D-Y, VAS Cosmesis, complications and economics questionnaire
6 months	PROMIS UE, Wong-Baker, EQ-5D-Y, VAS cosmesis, complications and economics questionnaire
1 year	PROMIS UE, Wong-Baker, VAS cosmesis, Satisfaction score, EQ-5D-Y, complications and economics questionnaire.
1 year (recruitment centre)	All routinely available radiographs documenting the course of this injury will be collected from the patient record.
2 year	PROMIS UE, Wong-Baker, EQ-5D-Y, VAS Cosmesis, complications
3 year	PROMIS UE, Wong-Baker, EQ-5D-Y, VAS Cosmesis, complications. Any further routinely available radiographs documenting the course of this injury will be collected from the patient record.

Table 2 Data collection time points

9.2. Recruitment

We recognise that, unlike amongst adults, 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.[16] The expected recruitment rate will be adapted to accommodate this large seasonal variation. Hospitals identified to be recruiting sites for this study treat between 15 and 50 eligible cases per year. Recruitment rates in other paediatric trauma studies have shown to be as high as 85%. We have opted for a more conservative rate of 50% as studies comparing a surgical with a non-surgical group tend to experience higher rates of patients/parents declining participation. We anticipate achieving an average conservative rate of 0.8 patients per centre month.

Appropriate target recruitment rates for the internal pilot will be discussed with both TSC and the DSMC during the early stages of the trial.

We expect recruitment rates to vary between 0.7 (winter) and 2.5 (summer) patients per centre month through the year. Over the course of the 9 months internal pilot phase between April 2020 and December 2020, we expect that approximately 130-140 patients will be recruited from the 15 pilot centres. We will employ the following traffic-light stop/go criteria with regards proceeding to the full trial: RED: Recruitment falls below 100 patients – unless there are mitigating circumstances, determine that recruitment is not feasible and decide not to proceed; AMBER: Recruitment between 100-130 patients – Review recruitment strategies, report to TSC and NIHR HTA and continue with a modified recruitment strategy and intensive monitoring. GREEN: Recruitment exceeding 130 patients – proceed with study. Following the pilot phase, a minimum of 32 sites will be involved with recruitment, which will be completed within 16 months.

Recruitment will be maximised using the combined experience of the BOSS Collaborative Research Group, the OTS, and the PERUKI network as well as an embedded comprehensive qualitative component (described below). The aforementioned networks have a nationwide reputation for high recruitment within NIHR studies. The BOSS collaborative, directed by D. Perry (Chief Investigator), is a nationwide group of over 300 children's orthopaedic surgeons who have experience in recruitment to NIHR studies (BOSS rare disease study runs in 143 hospitals), and are now delivering the HTA studies SCIENCE and FORCE. The OTS, led by M. Costa (co-investigator), has extensive experience in delivering NIHR HTA funded trauma trials on time and target (DRAFFT, FixDT, WOLLF, WHIST). PERUKI, co-led by M. Lyttle (co-applicant) have a number of ongoing HTA trials (CAP-IT and FORCE).

9.2.1 Qualitative Study of Recruitment and Experience of Treatment Interventions

A qualitative study will be undertaken to identify barriers and facilitators to recruitment. The aim is to increase understanding of the impact of injury and inform practical strategies to improve the process of recruitment in the main trial, for example developments in the presentation of study information. In order to achieve this the study will explore: i) parent's and children's experience of injury, treatment and its impact on their daily life, ii) parent's and children's experience of being asked to participate in a randomised controlled surgical trial, and iii) staff experience of being involved in a paediatric surgical trial. In order to achieve this qualitative interviews will be incorporated in three phases of the study.

1) Set-up phase - Developing Trial Material (Pre/early Pilot) - Using existing PPI networks up to 10 parent/child dyads will be interviewed about their experience of a wrist fracture and thoughts/feelings about trial participation, Children will be involved in ways that are suitable for their age such as through using play, pictures or stories. An understanding of parent/child experience of injury, impact on their life and outcomes that are important to them will provide the context for exploring the acceptability of the

study. Their thoughts and feelings about the study will illuminate what they need to know in order to decide whether to take part in the study, how best to convey information, how they make sense of the study in light of randomisation, equipoise and preferences, and their concerns about the study. This work will inform further involvement with the Young Persons Advisory Group, Parents Advisory Group and parent/child co-applicants in the development of the explainer video, parent/child information and consent/assent sheets.

2) Internal pilot phase - Up to 20 parent/child dyads will be interviewed about their experience of injury and what it was like to take part in the trial during the first 3 months of treatment (the time at which the primary outcome will be measured). This will provide an understanding of i) what injury and early recovery is like for parents and children, ii) how they make sense of this study, iii) the acceptability of treatment, trial processes, parent/child information sheets and explainer video, and iv) what is important to them in early recovery. This evidence will be used to inform the main study to improve acceptability and facilitate recruitment to the trial. Children's experience captured through the use of play, pictures or storytelling will provide their perspective. Furthermore, parents/children who decline to take part in the trial will also be invited to take part in an interview. This interview will focus on their experience of injury, how they made sense of the study and factors that influenced their decision not to take part in the study.

In order to understand the context of recruitment to the study up to 20 multidisciplinary staff members from approximately five to seven sites will be interviewed about their experience of the trial and factors that help/hinder trial recruitment. This interview will build on previous work in adult trauma[24] that identifies the challenges of creating a research culture, variations in degree of equipoise and acceptability of randomisation in some clinical circumstances. Gaining an insight into these issues in a Paediatric context will provide direction for the main study.

3) Main study phase - Up to 20 parent/child dyads will be interviewed 3 -12 months post treatment at the end of the main-phase of the study (i.e. around 12 months post-treatment) about their experience of injury, treatment, recovery and reflections on taking part in the trial. Children's experience captured through the use of play, pictures or storytelling will provide their perspective. This will provide knowledge about parent/child important outcomes, such as body image, from later on in recovery. It may also identify outcomes of importance that are not covered by the outcome tools. A follow up study of fractures in adults (WOLLF UK) shows that patients struggle with the uncertainty of recovery, look and feel different from pre injury and have a changed sense of self.[25] How parents and children integrate injury and recovery into daily life will be used to inform the acceptability of the treatments overtime and the dissemination of the study findings.

Methods - The methodological approach will be phenomenology to enable parents of participants and if appropriate participants to talk about their lived experience in light of their personal, social and historical context. This has proved useful in trials of injury[24,26–30] as it allowed them to identify what it is like for them within the context of their lives. A purposive sample of parents of children will reflect a range of ages, gender, experiences and both treatments. The parent and, if appropriate, participant will be introduced to the main and qualitative study. Electronic consent to contact the parent and provision of contact details will be sought for those who either consent or decline consent to the main study. The parent will then be contacted by the qualitative research team and further detailed information about the sub study will be provided. Written or verbal consent/assent will be sought. Paper consent forms will be completed, if verbal consent is provided, this will be witnessed by a GCP trained professional. Paper copies of consent/assent forms for all interviews will be provided to the participant. A convenient time for the interview will be

arranged. Evidence of children's experience may be provided by parents, such as pictures, photographs, old plaster casts, quotes and stories. Interviews may take place via the telephone or computer link, in the home, in an appropriate clinic or alternative setting. To ensure personal safety the researcher will follow the Oxford Trauma lone working policy. Privacy and dignity of the parents/child will be considered at all times. Parents may be interviewed together or separately, with or without their child depending on preference. Children will always have at least one parent present. Parents will provide informed written consent for their and their child's interview. Verbal consent for parents who have a telephone interview will be witnessed by a GCP trained administrator. Children's willingness to take part will be determined by what they say and do, if able, children will provide informed written assent. Parents will make the decision if their actions are not transparent. If the parents/child become upset at any time the researcher will stop the interview and provide support. Parents and children can withdraw from the qualitative study at any time.

For parents the interviews will be lightly structured to cover how they and their child experience injury/recovery, how they make sense of the trial, acceptability of treatment, trial processes and materials (information sheet, explainer video), and important outcomes. Open questions will be used to ascertain what it has been like to have an injured child and for their child to be invited to take part in a trial. Prompts will focus on how they felt and what they thought. Theoretical sensitising concepts will be, understanding, randomisation, equipoise, preferences, therapeutic misconception, decision making. For children there will be age appropriate involvement through the use of play, drawing, photographs, writing and stories. Children may choose from a range of activities what they would like to do. These activities will be used to help the child tell the researcher about their experience. Older children 6-11 years are able to express how they feel, what they cannot do and describe their problems.[28] Field notes will be written as soon as possible after an interaction with a child to provide contextual/reflective data.

Interviews will be digitally audio recorded and transcribed verbatim. Data will be analysed inductively, which involves the investigator becoming immersed in the data, identifying codes or units of meaning, systematically grouping codes of similar meaning into categories, and drawing them together into themes by comparing within and across categories. Reflective discussion will occur throughout analysis and include the positionality of the researchers. PPI representatives will take part in a one-day analysis workshop during the study to explore the process of analysis, sensitise the researchers to the use of language, underlying ideas and different perspectives within the data. Qualitative data will be managed using NVIVO 11, a qualitative software package. Rigour will be demonstrated through trustworthiness,[31] including prolonged contact with the data, provision of an audit trail and reflexivity.

9.3. Screening and Eligibility Assessment

Patients will be screened from the Emergency Department and/or fracture clinics at the recruitment centres. All patients with radiographic evidence of a displaced fracture at the level of the physis or metaphysis will be screened and assessed for eligibility by a local research associate. Screening logs will be kept at 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.

9.4. Informed Consent

A member of the clinical team will initially approach the patient and their parent(s). 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 trial procedures. Age-appropriate paper information sheets are also available. The family will then be given the opportunity to discuss issues related to the trial with the research team, the treating clinician, and family and friends. The parent will then be asked to sign an electronic informed consent form and, where appropriate as assessed by the local research associate in collaboration with the parents, children will be asked for their assent. The absence of assent does not exclude the patient from the study if consent has been obtained from the parent/legal representative. However, if a child completes the assent form indicating that they do not wish to participate, the child will not be included in the study. 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 a paper copy of the completed consent/assent forms to give to the parent.

Any new information that arises during the trial that may affect parents' or participants' willingness to take part will be reviewed by the 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.

9.5. Randomisation

The patient will be randomised after consent and baseline data has been obtained, either in the emergency department, or at the first assessment in the fracture clinic. 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 computer randomisation service provided by OCTRU. Randomisation allocation will be implemented using a minimisation algorithm with stratification factors: centre, type of fracture translation (completely off-ended versus incompletely off-ended), fracture location (metaphyseal or physeal) and age group (4-6 years, 7-10 years). 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 centre will help to ensure that any clustering effect related to the centre will be equally distributed between the trial groups. Each hospital has a children's injury unit dealing with these wrist fractures on a daily basis. All of the recruiting hospitals, and all orthopaedic units throughout the NHS, use these techniques as part of their normal fracture management practice so staff will already be equally familiar with both forms of treatment. This cannot eliminate the clinician-specific effect of an individual at any one centre.[32] However, as the procedures are commonplace across the NHS, many clinicians (15-30 clinicians at each centre, including consultants and trainees) will be involved in the management of this group of patients. We therefore anticipate that each individual clinician will only treat a handful of those enrolled in the trial, which greatly reduces the risk of a clinician-specific effect on the outcome in any one centre.

Stratification by fracture severity (translation) will ensure that the treatments are balanced across the common patterns of severe children's wrist fracture (completely off-ended versus incompletely off-ended).

Stratification by fracture location will ensure that involvement of the physis (Salter Harris II vs. Metaphyseal) are balanced across treatment groups as fractures closer to the physis are believed to remodel fastest.

Stratification by participant age will also ensure balance, because younger children have better remodelling capacity than older children.

9.6. Blinding and code-breaking

Patients and their parents cannot be blinded to their treatment. The treating clinician also cannot be blinded to the treatment they are providing. However, the clinical team will not be involved in any part in the follow-up assessment of the patients. The outcome data will be collected directly from the patient and their parents.

9.7. Description of study intervention, comparator and study procedures (clinical)

All of the hospitals involved in this trial are familiar with both techniques. All of the patients will receive a temporary plaster cast and 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.[29] Randomisation will occur at the point where the treating clinician believes that the child would benefit from surgical reduction with or without fixation.

This trial will compare two approaches to treat displaced distal radius fractures in children aged 4-10 years old inclusive.

9.7.1 Non-surgical casting

This technique involves the application of a plaster cast to hold the bone fragments in the optimal possible 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 technique. A record will be made of the cast details and any cast changes. Usual practice is for the plaster cast to be used for 4-6 weeks.

9.7.2 Surgical Reduction

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. The method used to hold the bones in position will be at the discretion of the clinician; i.e. plaster cast alone, plaster cast and wires, plaster cast and plate. A record will be made of the operative details, the cast details and any cast changes. Following surgery, usual practice is for the arm 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.

9.7.3 Rehabilitation

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 6-week, 3-, 6- and 12-month follow-up datasets from both patients and clinical teams.

9.8. Baseline Assessments

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.

Baseline demographic data using the PROMIS instrument, Wong-baker Faces Pain Scale and EQ-5D-Y health-related quality-of-life questionnaire will be collected.

9.9. Clinic Visit

Participants will usually attend at least one visit to the orthopaedic or trauma clinic after their initial treatment as part of standard care. During this visit, approximately 4-6 weeks post-treatment, the clinical team will perform a clinical assessment and standard radiographs will be taken. The research team will record any early complications that have occurred.

At 12 months, the research team will transfer routinely collected images of the wrist that are collated within the PACS system. These will be transferred to the central office, where they will be assessed by an independent adjudication committee.

9.10. Remote follow-up (6 weeks, 3, 6 & 12 months)

At 6 weeks, 3, 6 & 12 months post-injury, and then annually for a further two years parents of participants will be contacted by the central study office and invited to complete the PROMIS, Wong-Baker, EQ-5D-Y, VAS Cosmesis, complications and resource use questionnaires. At one year, a satisfaction score will also be sent out.

The invitation will be sent to the participants' parents via email and/or SMS, according to their stated preference. A secure online link will be included in the email or SMS so that participants' parents can complete the questionnaires online.

Participants who do not complete the questionnaires within a specified time-frame will receive reminder emails and/or SMS and if this does not elicit a response, it will be followed up with a telephone call from the central study office. Exact timelines and frequency of phone calls will be specified in the data management plan.

9.11. Sample Handling

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

9.12. Early Discontinuation/Withdrawal of Participants

Children (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 patient receives. Children (or their parents) can withdraw by contacting the research team, with contact details on patient information materials and the trial website. Upon withdrawal of the patient, any data collected up until the time of withdrawal will be retained by the research team and included in the final analysis. Contact details for these patients will be destroyed. Withdrawn patients or patients deemed ineligible after consent will not be replaced.

9.13. Definition of End of Study

The end of the trial will be defined as the collection/receipt of the last follow-up questionnaire from the last participant.

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 12 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

A serious adverse event 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 a serious adverse event 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 serious adverse events (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 PI becoming aware of the event. Once

received, causality and expectedness will be confirmed by the Chief Investigator 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 1 working day, and the SAE is judged to be unexpected by any one of either the PI, Nominated Person or CI, the event will be classified as an Unexpected Event.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator 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 Chief Investigator 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 TSC and DSMC at their next meetings.

10.3. Management of Complications

Complications that are foreseeable in the treatment of these fractures do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. For this trial, such events include:

(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, scar problems (overgranulation/ hypertrophy/ keloid)), pain, and the need for hospital admission to manage these complications or further unplanned surgery in either group (including surgery for revision, 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.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

A separate statistical analysis plan (SAP) with full details of all statistical analyses planned for the data of this study will be drafted early in the trial and finalised prior to any primary outcome analysis. The SAP will be reviewed and will receive input from the TSC and DSMC. Any changes or deviations from the original SAP will be described and justified in the protocol, final report and/or publications, as appropriate. It is anticipated that all statistical analyses will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages.

11.2. Description of the Statistical Methods

Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and standard deviations or medians and interquartile ranges as appropriate for continuous variables and numbers and percentages for binary and categorical variables. All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals.

The PROMIS Upper Extremity Score for children at 3 months is the primary outcome of the study and will be compared between treatment groups as the dependent variable in a multivariable linear regression model, adjusting for the stratification factors. An unadjusted t-test will also be undertaken. Additional

analyses utilizing all the time-points (from 6 weeks to 1 year post-randomisation) using multi-level modelling will also be undertaken for completeness. Subgroup analysis by fracture type (metaphyseal and Salter-Harris II fractures) will be undertaken using the same methodology by incorporating a treatment by fracture type interaction. Multi-level, mixed effects repeated measures linear regression models will be used to analyse continuous secondary outcomes, if appropriate; otherwise, appropriate non-parametric alternatives will be used. Complications will be reported by type for each treatment group, and, if appropriate, compared between the groups using logistic regression models.

11.3. Sample Size Determination

674 participants providing data on the PROMIS Upper Extremity Score for children at 3 months post-treatment (337 in each group) will provide 90% power and 2.5% (1-sided) significance to detect whether non-surgical casting for the treatment of displaced wrist fractures is non-inferior to surgical reduction assuming a non-inferiority margin of -2.5 points, a standard deviation of 10 and no difference between groups (PASS 16 Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.). The choice of the non-inferiority margin and the baseline standard deviation have been based on discussions with patients, their parents and the literature validating the PROMIS Upper Extremity Score in a range of different diseases. Allowing for 10% loss to follow-up, this yields an overall target of 750 patients (375 per group).

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 'Minimally Clinically Important Difference' (MCID) for the PROMIS Upper Extremity Score amongst children with mild forms of disability has been demonstrated to be 3 or 4.[30] In general, the bank of paediatric PROMIS measures have an MCID of 3 points, in a range of different diseases including sickle cell anaemia/asthma/nephrotic syndrome/cancer.[33] We have worked with parents with upper limb injuries to re-score the PROMIS Upper Extremity tools for the vignettes to indicate 'the minimum difference that is likely to be noticeable', and 'the minimum difference that would be necessary to justify undertaking surgery'. Although a score of 4 points appeared to be the minimal difference noticeable to parents, the clinically important difference required to justify surgery was 5 points (standardised effect size > 0.5). Parents and children demanded a larger effect size to justify the intervention of surgery. Other studies have similarly highlighted that patients often seek greater effect sizes to warrant surgical interventions than the established MCID.[34] A non-inferiority margin of 2.5 points was decided upon as half the maximum tolerated reduction in acceptability to patients and their parents to justify surgery. If non-surgical casting is shown to be non-inferior based on this then the results of the trial are likely to change clinical practice for these fractures.

For non-inferiority, the lower 95% confidence interval of the treatment difference between non-surgical casting and surgical reduction is assessed against the non-inferiority margin of -2.5 points and, if it lies above this, then non-surgical casting will be found to be non-inferior to surgical reduction. If non-inferiority is shown then superiority will also be tested at the 2.5% (1-sided) significance level. In this case the lower 95% confidence interval would be above zero points.

As the degree of translation has the potential to influence outcome, we have incorporated this as a stratification factor to ensure that it is balanced across the treatment groups and we will assess for differential outcomes in the important subgroups using treatment-by-subgroup interactions. From the site audits approximately a quarter to a third of these fractures will be completely off-ended. This implies that from the 750 total patients recruited, 200-250 patients will have completely off-ended displaced fractures.

This is an important subgroup for surgeons as this represents the most severe fractures. Collecting 200 patients within this subgroup will enable non-inferiority for non-surgical casting with surgical reduction assuming 90% power, 2.5 (1-sided) significance with a non-inferiority margin of between -4.5 to -5 points on the PROMIS Upper Extremity Score for Children at 3 months assuming a standard deviation of 10. This is above the maximum tolerated reduction in acceptability to patients and their parents to justify surgery. We therefore plan on continuing recruitment until a minimum 200 patients in the completely off-ended subgroup have been randomised. Fracture location (metaphyseal vs. physeal) and participant age also has the potential to influence outcome, and we have also incorporated these as stratification factors to ensure that these are balanced across the treatment groups.

11.4. Analysis populations

Since this trial uses a non-inferiority design, the primary analysis of the primary outcome will be based on the per-protocol (PP) population. This population will include all patients who received their allocated treatment, and did not have any major protocol deviations. Major protocol deviations will be finalised following a blinded review of the data prior to the primary outcome analysis data-lock.

A secondary analysis will be undertaken on the intention-to-treat (ITT) population. This will include all randomised participants with available data who will be analysed according to their allocated intervention regardless of the treatment they received.

All analyses of the secondary outcomes will be performed for the ITT population.

11.5. Decision points

The decision to continue to the main part of the trial after completion of the internal pilot is described in section 9.2 (recruitment)

The SD of 10 derived by PROMIS was ascertained based on a sample of children with a higher proportion of chronic illness than the general population and it is anticipated that the variation in outcomes in the treatment of displaced distal radius fractures may be less than in a chronic illness. Therefore, we propose to undertake a blinded sample size assumption review once a minimum of 50 participants have completed the primary outcome measure at 3 months. The results of this will be reviewed by the DSMC, including the SD to see if it is substantially different from that expected, and they will make recommendations regarding the final sample size to the TMG and TSC. We will discuss the potential impact of the recommendations on study timelines with the TSC to determine the optimal study duration, thereby enhancing the efficiency of the trial. This review is likely to coincide with the end of the internal pilot phase of the trial.

11.6. Stopping rules

Given that this is a trial of interventions already routinely offered in the NHS, no formal stopping rules will be employed. Over the course of the trial, the DSMC will review related serious adverse events (SAEs) and interim trial results at pre-determined intervals. The frequency and severity of SAEs will be reviewed by the committee to ascertain safety of the interventions. Interim trial results will be assessed for early indicators of significant superiority/inferiority of one of the proposed treatment. After each review, the DSMC will put forward its recommendation with regards study continuation to the TSC.

11.7. The Level of Statistical Significance

One-sided 2.5% significance will be used for the non-inferiority comparisons – this translates into a comparison of the lower bound of the 95% confidence interval being compared with the non-inferiority margin. For the superiority comparison and secondary outcome analyses 5% (2-sided) significance will be used. 95% confidence intervals will be reported throughout.

11.8. 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. The primary analysis of the primary outcome 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.

11.9. 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.

11.10. Health Economics Analysis

An economic evaluation of surgery versus cast immobilisation will be conducted from the UK NHS and Personal Social Services perspective (PSS)[35] using the CRAFFT trial data. A Health Economics Analysis Plan (HEAP), providing full details of the prospective economic analysis, will be finalised before the end of follow-up.

Health related quality of life will be estimated using the EuroQol EQ-5D-Y.[22,23] EQ-5D-Y responses will be valued using the most appropriate valuation set available for the trial population at the time of analysis. If necessary the adult EQ-5D-3L will be applied, in which case we will undertake sensitivity analysis to make sure that trial findings are not sensitive to the valuation set chosen.[36] Using the trapezoidal rule, the area-under-the-curve of health status scores will be calculated, providing patient-level QALY estimates.

Participants' health service contacts, made in connection with the child's injury, will be recorded at 6 weeks, 3, 6 and 12 months. Index interventions and subsequent healthcare resource use will be costed using most recently available published national reference costs, reflated to a common year[37,38] Parents/Carers out-of-pocket expenses and time lost from work (paid/unpaid) because of their child's condition and time off from school will also be recorded. Resource use questionnaires will be completed by each child's parent/carer as a proxy response.

Mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data. Imputation sets will be used in bivariate analysis of costs and QALYs to generate within-trial (12 month) incremental cost per QALY estimates and confidence intervals[39–42]. Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. If incremental costs and benefits are non-convergent within the trial follow-up then extrapolated modelling will be considered, drawing upon epidemiological sources. Sensitivity analyses will be conducted to consider the broader issue of the generalisability of the study results and consider the impact of a broader societal perspective.

12. DATA MANAGEMENT

The data management aspects of the study 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, microfiches, 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 study-specific documents, other than the signed consent, the participant will be referred to by the study 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 and host institution for monitoring and/or audit of the study. The data submitted by trial participants directly to the Sponsor via the clinical database (i.e. electronic patient reported outcomes) will also be made available to the participating site.

12.3. Data Recording and Record Keeping

The case report forms will be designed by the trial manager in conjunction with the trial management team. Patients' parents/guardians 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 this additional data reduces loss to follow-up substantially.

Data will be collected in electronic format with direct entry onto the trial database; including the collection of documentary evidence of consent and assent. 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 (Research Electronic Data Capture) 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[38,39]. Wherever possible, trial data will be entered directly into the trial database by site staff or participants. 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 entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the study. 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 public to see on the study website.

Paper forms, e.g. qualitative consent/assent forms, if collected, with patient/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 patients (both paper and electronic). Patients 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. All paper and electronic data, including Consent/Assent forms will be retained until the youngest participant reaches 21 years of age. Contact details will be retained until the long term follow up is complete (3 years after randomisation).

Digital audio recordings of qualitative interviews will be electronically transcribed by the central research team at the University of Oxford, and the anonymised transcriptions will be stored on secure servers at the University of Oxford until the youngest participant reaches 21 years of age. The audio recordings will be deleted at the end of the main study.

The trial will be reported in line with the CONSORT statement and the appropriate extensions including non-pharmacological and patient reported outcomes.

Data on paper forms or captured during phone calls to participants will be entered into the trial database by suitably trained central office staff. Full details will be recorded in the Data Management Plan. The participants will be identified by a unique trial specific number in any data extract. Identifiable data will only be accessible by members of the study 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).

13. QUALITY ASSURANCE PROCEDURES

This study will be coordinated by the by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. A rigorous programme of quality control will be implemented. The trial management group will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. The OCTRU has a quality assurance manager who will monitor this trial by conducting inspections (at least once in the lifetime of the study, more if deemed necessary) of the Trial Master File. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the trials unit staff. Written reports will be produced for the TSC, informing them if any corrective action is required.

Additionally, the study 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 study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Quality control procedures will be undertaken during the recruitment and data collection phases of the study 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. Study Committees

13.3.1 Trial Management Group

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager. This will be overseen by the TMG, who will meet monthly to assess progress. A Patient and Public Involvement (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

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 study 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 11.6 for details). DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

14. PROTOCOL DEVIATIONS

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

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice 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 study 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 study 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 (where required) 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 study 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 study, particularly a study involving randomisation, may be a concern for some parents. The research associates at the recruitment centres have all got extensive experience in working with children and parents. Any specific concerns that may arise during the qualitative interviews will be discussed by the trial management group and appropriate changes to the information presented to parents and their children will be made.

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 and our PPI advisors and Jenny Preston (who leads PPI across NIHR CRN Child)). 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 this content, it was felt that a single simplified information leaflet may be useful for sites to use (at their discretion) to frame the conversation around consent. Parent co-applicants and members of the Parents Advisory Group have identified the key information that they wish to have available in this simplified document, and which they would like to be able to access only online (i.e. some elements of data protection and GDPR). We will ensure that the full trial details (i.e. in a conventional PIS format) are available for download on the trial website in a parent and child format.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same 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.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and 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 study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

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.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (NIHR127674). 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

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties; a contract will be drawn up between the Department of Health and the University of Oxford. Further collaboration agreements will be completed between the University of Oxford and the Universities of Warwick and West England as well Sheffield Children's and Cambridge University Hospitals NHS Foundation trusts.

18. PUBLICATION POLICY

The study monograph will be prepared by the trial management team when the primary end point is completed (one year follow up) and a further publication will occur at completion of the trial. No patient identifiable information will be contained in any form of dissemination of study 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 surgeons, 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 non-complex fracture guidelines, and will be directly relevant to the widely publicised Choosing Wisely Campaign.
- 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 will produce an initial Wikipedia page for this injury (currently missing) 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.

21. HISTORY

Version and date	Significant changes from previous version
V1.0_28Jan2020	Not applicable as this is the 1st issue
V2.0_13Aug2020	Minor grammatical errors corrected. Addition of ethics, ISRCTN and NIHR CRN Portfolio reference numbers. 6.1. Outcome measures: Addition of details on assessment of cosmesis & parent satisfaction. 9.1. Data Collection: Addition of email tracking system and resolution of data queries; removal of GP contact for data queries. 9.7.3 Rehabilitation: Prescribed rehabilitation written advice removed. 9.8. Baseline Assessments: Secondary contact details to be deleted if consent is not given to keep these details 10. Safety Reporting: Addition of time-frame by which SAEs should be reported; addition of types of causality; addition of details on the complications (expected SAEs). 11.10 Health Economics: Changes in section and reference to the HEAP added. 13. Quality assurance procedures: Recognition of OCTRU via which the study will be coordinated.

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