Protocol for Surgery or Cast of the EpicoNdyle in Children's Elbows (SCIENCE)

a multicentre prospective randomized superiority trial of operative fixation versus non-operative treatment for medial epicondyle fractures of the humerus in children

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Aims

The management of fractures of the medial epicondyle is one of the greatest controversies in paediatric fracture care, with uncertainty concerning the need for surgery. The British Society of Children's Orthopaedic Surgery prioritized this as their most important research question in paediatric trauma. This is the protocol for a randomized controlled, multicentre, prospective superiority trial of operative fixation versus nonoperative treatment for displaced medial epicondyle fractures: the Surgery or Cast of the EpicoNdyle in Children's Elbows (SCIENCE) trial.

Methods

Children aged seven to 15 years old inclusive, who have sustained a displaced fracture of the medial epicondyle, are eligible to take part. Baseline function using the Patient-Reported Outcomes Measurement Information System (PROMIS) upper limb score, pain measured using the Wong Baker FACES pain scale, and quality of life (QoL) assessed with the EuroQol five-dimension questionnaire for younger patients (EQ-5D-Y) will be collected. Each patient will be randomly allocated (1:1, stratified using a minimization algorithm by centre and initial elbow dislocation status (i.e. dislocated or not-dislocated at presentation to the emergency department)) to either a regimen of the operative fixation or non-surgical treatment.

Outcomes

At six weeks, and three, six, and 12 months, data on function, pain, sports/music participation, QoL, immobilization, and analgesia will be collected. These will also be repeated annually until the child reaches the age of 16 years. Four weeks after injury, the main outcomes plus data on complications, resource use, and school absence will be collected. The primary outcome is the PROMIS upper limb score at 12 months post-randomization. All data will be obtained through electronic questionnaires completed by the participants and/or parents/guardians. The NHS number of participants will be stored to enable future data linkage to sources of routinely collected data (i.e. Hospital Episode Statistics).

Bone & Joint Open

Take home message

- The SCIENCE study will provide a definitive answer for the optimal treatment of displaced medial epicondyle fractures in children.
- The SCIENCE study has been instrumental in improving the international infrastructure for developing high-quality evidence within children's orthopaedic surgery.

Introduction

The management of fractures of the medial epicondyle is one of the greatest controversies in paediatric fracture care.[1] These fractures typically occur in children aged around ten to 12 years,[2] with or without dislocation of the elbow joint. The debate for clinicians is whether to realign and hold the fragments of bone with operative fixation, or to allow the fragments to heal in their current position, without surgery, by resting the elbow in a cast. Observational studies have demonstrated support for both operative and non-operative treatment strategies, which has generated uncertainty among surgeons.[2,3] However, the current literature has serious methodological limitations, particularly with regard to inconsistent follow-up, no standardization to the treatment approaches, the infrequent use of patient-reported outcomes, and selection bias among those chosen to undergo operative fixation.[3]

The indications among those receiving surgery vary considerably. There is agreement that operative intervention to realign the bones is suitable in instances where the fragment of medial epicondyle is trapped in the joint, or where the elbow is dislocated. However, beyond these relatively rare indications, the usual indication for surgery is radiological displacement of the fracture fragments beyond a surgeon-dependent threshold varying between 2 mm and 15 mm;[4,5] however, radiographs on which this assessment is made are known to be hugely misleading, with 'minimally displaced' fractures frequently having > 10 mm displacement evident when using 3D imaging.[6,7] The degree of displacement, either initially or after healing, has not been shown to affect the outcome of treatment. In instances where the fracture is associated with an elbow dislocation, and the elbow can be readily reduced, there is controversy whether this necessitates fixation irrespective of the degree of fracture displacement, however a recent systematic review did not find evidence to support this approach.[8]

Despite the uncertainties, there has been an increasing tendency toward surgery for this fracture, which has been particularly driven by the athletic demands of children and adolescents, and the expectations of patients, parents, and coaches, of early mobilization and return to sport.[1,9] Surgical fixation, using either a wire or a screw, is thought to improve the likelihood of 'bony union' of the fracture (approximately 50% vs 95%),[2] though it is unclear if this has any bearing on functional recovery, including return to sports. However, there are small but definite risks from the surgery including infection, damage to the nerves around the elbow, broken and retained metalwork, and the risks associated with general anaesthesia. While possibly increasing the speed of recovery, there is some suggestion that those for whom the fracture has been treated operatively compared with nonoperatively may have more long-term pain.[10] Additionally, following initial surgery, a second surgery is frequently performed at a later stage to remove the metalwork used for the fixation owing to skin irritation. The alternative treatment of temporary immobilization does not expose the child to the same surgical risks, and has lower costs.

There is therefore a clear and pressing need to inform patients about the benefits or otherwise of operative fixation versus nonoperative treatment, and a need to inform commissioners regarding the costs of the different treatment strategies to the NHS and society.

To summarize, there are two broad management strategies for the treatment of displaced medial epicondyle fractures, involving operative fixation or non-surgical treatment. Surgery may promote early function and bone union, but concern remains about the potential complications of surgery, the need for secondary surgery, and possibility of ongoing pain. This is the protocol of a randomized superiority trial of operative fixation versus nonoperative care.

The Surgery or Cast of the EpicoNdyle in Children's Elbows (SCIENCE) trial will be reported in line with the CONSORT statement using the non-pharmacological treatment interventions and patient-reported outcomes extensions.[11]

Aims

The aim of this pragmatic randomized controlled trial is to evaluate the clinical and cost-effectiveness of operative fixation versus nonoperative treatment for displaced medial epicondyle fractures of the elbow in children.

The primary objective is to quantify and draw inferences on observed differences in function using the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Limb Score for Children between operative fixation versus nonoperative treatment at one-year post-randomization for fractures of the medial epicondyle in children.[12,13]

The secondary objectives are to quantify and draw inferences in observed differences between treatment groups, related to: 1) function using the PROMIS Upper Limb Score; 2) sports and performing arts participation using the Sports/Performing Arts (s/PA) Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) Module (a validatded assessment of higher-level upper limb function);[14] 3) pain using the Wong-Baker faces pain score;[15] 4) quality of life using the EuroQol five-dimension questionnaire for younger patients (EQ-5D-Y) (a validated assessment of childhood health-related quality of life); 5) complications, including the need for further operative interventions; and 6) cost-effectiveness of the two treatments to the NHS and, more broadly, society.

A schedule of data collection is outlined in Table I.

To determine the most appropriate primary outcome, we discussed the proposed trial with children and families, and consulted 15 members of the GenerationR NIHR young person's advisory group (YPAG). Children indicated that function was the most important outcome, particularly the long-term function, with early return to function a secondary concern. Parents were similarly concerned by pain, function, and in addition, the duration of school absence. With input from these groups we resolved to measure function at 12 months post-randomization as the primary outcome, measuring function (including sports/musical instrument

Table I. Outcomes collection schedule.

Timepoint	Data collection
Prior to randomization	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y
4 weeks (routine follow-up)	Complications
6 weeks (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y, complications, and school attendance
3 months (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y, complications, school attendance, and resource utilization
6 months (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y, complications, school attendance, and resource utilization
1 year (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y, complications, school attendance, and resource utilization
Annual until skeletal maturity (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5D-Y, complications (UK only)
Long term (electronic linkage)	Linkage through routine datasets to determine relevant interventions (i.e. elbow arthroscopy/ arthroplasty) (UK only)

DASH S/PA, Sports/Performing Arts module of the Disabilities of the Arm, Shoulder and Hand questionnaire ; EQ-5D-Y, EuroQol five-dimension questionnaire for younger patients; PROMIS, Patient-Reported Outcomes Measurement Information System.

participation) at interval periods during the first year after injury. We also agreed to follow the children in the longer term, to ensure that there was no long-term sequalae of injury or treatment.

The primary outcome for this study is the functional recovery assessed using the Patient Report Outcomes Measurement Information System (PROMIS Bank v2.0) Upper Limb Score for Children Computer Adaptive Test (CAT) – PROMIS is 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 USA National Institutes for Health.[12,13] These tools can be administered to healthy children, as well as to children with a variety of chronic health conditions. They are generally self-reported from the age of eight years, and proxy-reported below eight years. The PROMIS Paediatric item banks were developed using a strategic item generation methodology adopted by the PROMIS Network using item response theory. Field-testing occurred among 4,129 children aged eight to 17 years old.[16] All raw scores generated from PROMIS instruments are translated into standardized T-scores with a population mean of 50 and a standard deviation (SD) of 10. The population mean refers to the mean of the calibration sample, which, for paediatric and parent proxy instruments, is composed of a higher percentage of patients with chronic illness. Lower T scores indicate a worse outcome for upper limb function. PROMIS is available in full (30 questions), short-form (eight questions), or as a computer adaptive test 'CAT' (average eight questions). A CAT enables the answer from one question to inform the choice of the next so that each child completing a CAT could answer a distinct set of questions to arrive at their score.

The secondary outcome measures in this trial are as follows:

Sports/Performing Arts Module of DASH:[14] This is a tool for recording details of sports and performing arts participation relating to upper limb function. Although not specifically developed in children, there was universal agreement, among children present at an 'Elbow Study Day' and members of the NIHR YPAG, that the language in this tool was appropriate for use among children who are able to comprehend other self-reported questionnaires used in this study.

Wong-Baker FACES Pain Rating Scale:[15] This is a validated self-reported ordinal assessment of pain using a series of six facial expressions to illustrate pain intensity. A numerical rating is assigned to each face (from 0, "no hurt" to 10, "hurts worst"). It has been validated for use among children from five years old.[17,18] It is highly correlated to the visual analogue scale (r = 0.90, $p < 0.001$)[19] and is widely used in clinical practice, forming part of the Royal College of Emergency Medicine 'Composite tool for the assessment of pain in children,'[20] and recommended in the NICE major trauma guidelines.[21]

Quality of life (EQ-5D-Y): This is the child-friendly version of the EQ-5D-3L, which has been adapted in terms of language for children aged eight to 11 years and for adolescents aged 12 to 18 years.[22,23] A proxy version is available for younger children. Its age appropriateness in terms of feasibility, reliability, and validity in children and adolescents has been established.[24]

Complications: all complications will be recorded. Particular note will be made of complications related to the cast (e.g. pressure areas) or surgery (e.g. pain, wound infection, injury/irritation to the ulna nerve, implant irritation, screw cut-out, broken or retained metalwork, and the subsequent need to remove metal pins/screws), including hospital admission to manage these complications.

Radiographs: digital images of the elbow that have been collected as part of routine practice will be harvested from a picture archiving and communication system, including those collected preoperatively, intraoperatively (where relevant), and the last available follow-up image (i.e. the most recent image collected prior to the one-year primary outcome point.

Healthcare use: This will be monitored for the economic analysis. Hospital and community healthcare visits, medication, parent/guardian lost productivity, missed schooling, and out-of-pocket expenses will be recorded via a short questionnaire which will be administered at three, six, and 12 months post-randomization completed by the parents/guardians.

Sample size

The primary outcome is the PROMIS Upper Limb Score for Children. Raw scores are translated into standardized T-scores with a population mean of 50 and a SD of 10. The minimal clinically important difference (MCID) for the PROMIS Upper Limb Score among children with milder forms of disability has been demonstrated to be three to four.[24] In general, the bank of paediatric PROMIS measures have a MCID of three points, in a range of different diseases including sickle cell

disease, asthma, nephrotic syndrome, and cancer.[25] During a patient and public involvement event, it was established that while a score of three to four points appeared to be the minimal difference noticeable to parents, the clinically important difference required to justify surgery was five points or more. 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.[26] We seek to find a difference of four points between the interventions.

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. It is anticipated that the variation in outcomes in the treatment of acute medial epicondyle fractures is likely to be less than in a chronic illness. Therefore, blinded sample size re-estimation, based on the SD of the outcome tool when patient recovery is beginning to plateau, is planned. We will perform the sample size re-estimation calculation after the first the 50 patients have completed six months' follow-up (estimated to be month nine of the main trial). If, as expected, the SD of the sample is notably less than the chronic disease population, we will revisit the study timelines to determine the optimal study duration, thereby enhancing the efficiency of the trial. In the unlikely event that the SD is greater than expected, we will discuss the findings with the trial steering committee to formulate a strategy to meet the increased recruitment target required.

In summary, this study will use the PROMIS Upper Limb Score for Children at one year after randomization as the primary outcome measure. The total number of patients required to obtain a power of 90% to detect a four-point difference between groups for the primary outcome measure will be 266, i.e. 133 patients will be required in each treatment group. With an allowance for a conservative 20% loss to follow-up, we plan to recruit 334 patients in total. To maximize trial efficiency, we will re-estimate the sample size based on the SD of the outcome tool at six months' follow-up of the first 50 children in the trial.

Methods

Children will be eligible for inclusion into the trial if there is radiological evidence of a displaced medial epicondyle fracture of the humerus, with fracture displacement determined by the surgeon as per their usual clinical practice; and they are aged between seven and 15 years inclusive.

Children will be excluded from this trial if the injury is more than two weeks old; there is incarceration of the medial epicondyle fragment within the elbow joint; the injury is part of a complex elbow fracture (i.e. fracture extending into the joint); there are other fractured bones elsewhere in the body, in addition to the elbow injury; the elbow, if dislocated, is unable to be realigned into a satisfactory position in the emergency department; and there is evidence that the patient and/or parent/guardian 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 to the internet.

Consenting

Recruitment will take place in a minimum of 30 NHS trusts who treat children with this injury in the UK, plus additional centres in New Zealand and Australia. Potentially eligible patients will be identified by the clinical team. The research associate will present the patient and parents/guardian with age-appropriate participant information sheets or online study information and a verbal explanation of the trial procedures. The patient/parent/guardian will then be given the opportunity to discuss any issues related to the trial with the research associate and members of their family and friends.

The parent/guardian will then be asked to sign an electronic informed consent form. Children will be invited to sign an electronic assent form (UK and New Zealand). In Australia, mature children (i.e. ≥ aged 13 years, or as decided by the research team) will be invited to sign an electronic consent form. Assent should be taken, where appropriate, however the absence of assent does not exclude the patient from the study if consent has been obtained from the parent/guardian. If a child indicates indicates they do not want to take part, they will not be included in the study.

In the UK, contact details will be retained until the long-term follow-up is complete (when the child reaches skeletal maturity at 16 years of age). Consent/assent forms will be kept until the youngest participant reaches 21 years of age.

In Australia and New Zealand, contact details will be retained for a minimum of one year after the 12-month follow-up period is complete. Completed parent consent and child consent and/or assent forms will be kept until the youngest participant reaches aged 25 years (Australia) or aged 26 years (New Zealand).

Randomization

Those patients who consent to take part in the trial will have their treatment allocated using a secure, centralized, online randomization service. All hospital treatment areas have access to the internet, so will access the randomization service in real time, i.e. there will be no delay in patient treatment.

Consented participants will be randomized to one of two intervention groups (1:1) using a computer randomization service provided by the Oxford Clinical Trials Research Unit (OCTRU). Randomization will be performed using a minimization algorithm, including a random element to ensure balanced allocation of participants across the two treatment groups stratified by centre and dislocation status of the elbow at presentation (i.e. dislocated or not dislocated). The first 30 participants will be randomized using a simple randomization schedule produced by the trial statistician, to seed the minimization algorithm, and a non-deterministic probabilistic element will be introduced to prevent predictability of the treatment allocation.

Stratification by centre within the minimization algorithm will help to ensure that any clustering effect related to the centre will be equally distributed in the trial arms. The catchment area (the local population served by the hospital) will be similar for all of the hospitals, each hospital being a children's injury unit dealing with these fractures on a daily basis. All of the recruiting hospitals use these techniques as part of their normal practice, i.e. 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. However, since the procedures are commonplace, many clinicians will be involved in the management of this group of patients – likely between five and 20 clinicians at each centre, including consultants and trainee surgeons. Therefore, we anticipate that each individual clinician will only treat a handful of those enrolled in the trial, reducing the risk of a clinician-specific effect upon the outcome in any one centre.

Stratification by dislocation status of the elbow (i.e. not dislocated at presentation to the emergency department, or dislocated at presentation to emergency department (with a subsequent satisfactory reduction)) within the minimization algorithm will help to ensure that the perceived severity of the injuries through additional soft-tissue damage are balanced across the treatment groups, to take account of the potential differences in the outcome measures. Any participants with an elbow dislocation that is unable to be reduced prior to study enrolment will be excluded from the trial.

Post-randomization withdrawals

Children (or their parents/guardians) 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/guardians) 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.

Blinding

Patients and their parents/guardians cannot be blinded to their treatment. The treating clinician will, of course, not be blinded to the treatment they are providing. However, the treating clinical team will take no part in the follow-up assessment of the patients. The outcome data will be collected directly from the patient and/or their parents/guardians. Outcome assessors will be blinded to the participant's treatment allocation.

Trial treatments

This trial will compare the two common approaches to treat a displaced medial epicondyle of the humerus in children, as follows.

In operative fixation, children are admitted to hospital for surgery, which is typically scheduled on a daytime trauma operating session, though patients can be enrolled irrespective of the time of presentation/surgery. Children undergo a general anaesthetic. After the skin has been covered in antiseptic, an incision will be made over the medial epicondyle paying particular attention to the location of the ulna nerve. The bone fragments will be opposed in the optimal position achievable under direct vision. A record will be made of the type of fixation used. The bone fragments will be fixed using the preferred technique of the surgeon (i.e. screw/wire(s)). Although the basic principles of fixation are inherent in the technique, there are several different options available to the surgeon, with the most common being screw fixation. The type of implant, size, and insertion technique are not believed to affect the outcome, and will be left entirely to the discretion of the surgeon as per their normal practice. At the end of the procedure, a sling, plaster, splint, or bandage will be applied as per the standard surgical practice. The elbow will be allowed to mobilize as per the usual practice of the treating surgeon under the direction of the clinical team, though fixed immobilization in a cast should not be used for more than four weeks post-randomization.

Nonoperative treatment involves immobilization of the elbow to rest it at around 90° of flexion. The immobilization device (i.e. cast, splint, bandage) is not applied with the intention of directly opposing the bone fragments, and therefore the bone fragments will not align perfectly. In this pragmatic trial, the duration and method of immobilization will be left to the discretion of the treating surgeon as per their usual technique, and will be worn as per the standard practice of the treating surgeon. Subsequently, the elbow will be allowed to mobilize as pain allows, under the direction of the clinical team. Fixed immobilization in a cast should not be used for more than four weeks post-randomization.

In this pragmatic trial, any rehabilitation input, including a formal referral to physiotherapy, 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 or interventions will be requested as part of the four-week, six-week, three-month, six-month, and 12-month follow-up datasets from both patients and clinical teams.

Adverse event management

Serious adverse events (SAEs) will be entered onto the SAE reporting form and reported to the central study team. Once notified, causality and expectedness will be confirmed by the chief investigator or trial-nominated clinician. Some adverse events that are foreseeable as part of the proposed treatment will not be reported on a SAE reporting form; they will be recorded on a complications reporting form. These events include: a) general complications – pain, pressure areas or elbow stiffness, symptomatic instability, or nonunion of the bone fragments; and b) complications specifically related to surgery – wound infection, injury/irritation to the ulna nerve, implant irritation, screw cut-out, broken or retained metalwork, and the subsequent need to remove metal pins/ screws.

All participants experiencing SAEs will be followed up as per protocol until the end of the trial. All unexpected SAEs or suspected unexpected serious adverse reactions (SUSARs) that occur between the date of consent and six weeks' follow-up point will be reported to the sponsor and ethics committee (as per the specifications set out by individual countries).

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

Analysis

Statistical analysis

A separate statistical analysis plan (SAP) with full details of all statistical analyses planned for the data has been produced

and will be made publicly available. The SAP has been reviewed and received input from the relevant institition's Trial Steering Committee (TSC) and Data Safety Monitoring Committee (DSMC).

Any changes or deviations from the original SAP will be described and justified in any updated versions of the SAP, protocol, final report, and/or publications, as appropriate. It is anticipated that all statistical analyses will be undertaken using Stata (StataCorp, USA) or other well-validated statistical packages.

All analyses will be carried out on the intention-to-treat population (that is, all patients will be analyzed in the group they were randomized to, regardless of actual treatment received). To test robustness of the results, sensitivity analyses that supplement the primary analysis will include repeating the primary analysis for the per-protocol population (patients excluded from the per-protocol population will be pre-specified in the SAP) and the as-treated population, bearing in mind that this may introduce bias by losing the benefits of randomization.

The PROMIS Upper Limb Score for Children at 12 months is the primary outcome of the study, and the primary analysis will compare this between the treatment groups in a linear mixed effects method including all patients, at all timepoints, and adjusting for the stratification factors. A simple analysis of covariance (ANCOVA) of the primary outcome at 12 months adjusting only for the baseline PROMIS score will be undertaken as a secondary analysis. If the outcome is not normally distributed, non-parametric techniques will be used with no adjustment (for example the Mann-Whitney U test or the Kruskal-Wallis test).

Although we have allowed for up to 20% missing data in the sample size, we hope to minimize this by using data collection techniques appropriate to the age of participating children. Before carrying out the within-trial analysis, we will check the trial data for any missing data. Where possible, the reasons for missing data will be ascertained and reported. The nature and pattern of the 'missingness' will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed using multiple imputation. The resulting imputed datasets will be analyzed and reported, together with appropriate sensitivity analyses.

Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and SDs, or medians and interquartile ranges (IQRs), 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 (CIs), and all tests will be carried out at a 5% two-sided significance level.

Health economic evaluation

An economic evaluation will be conducted as part of the trial to estimate cost-effectiveness. A health economics analysis plan (HEAP), providing full details of the prospective economic analysis, has been produced and will be made publicly available.

Since the trial is recruiting internationally, the analysis will be limited to UK recruiting sites and follow intention-to-treat principles. The main analysis will adopt an NHS and personal social services perspective. Participants are aged seven to 15 years, thus questions will be primarily completed or assisted by parents/carers.

Healthcare resource use will be costed using the most recently available published national reference costs, reflated to a common year. Index hospital procedures and any sequelae procedures will be costed using OPCS-4 codes and applying reference costs via the NHS Healthcare Resource Group (HRG) grouper.[27,28] Participants' health service contacts, made in connection with their elbow, will be recorded at three, six, and 12 months and costed using national unit costs.[28,29] Personal expenses, parent/carer time from work, and time from school will also be recorded as part of a broader societal perspective.

Generic health-related quality-of-life will be assessed at baseline, six weeks, and three, six, and 12 months using the EQ-5D-Y questionnaire. EQ-5D-Y scores will be converted to health status scores using the most appropriate tariff available at the time of analysis.[30,31] Using the trapezoidal rule, the area under the curve of health status scores will be calculated, providing patient-level quality-adjusted life year (QALY) estimates.

If overall data missingness exceeds 5%, the primary analysis will include multiple imputation using the MI framework in Stata. Mechanisms of missingness of data will be explored, and multiple imputation methods will be applied to impute missing data, following best practice.[32–34] Imputation sets will be used in bivariate analysis of costs and QALYs to generate incremental cost per QALY estimates and CIs. If the level of missingness is low, then a complete-case bivariate analysis will be conducted without imputation.

Findings will be analyzed and visualized in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit, and value of information analysis. A within-trial analysis will use the first 12 months of data, to correspond to the primary analysis. If incremental costs and benefits are non-convergent within the trial follow-up, then extrapolated modelling will be considered.

Trial oversight

The trial will be conducted in accordance with the Medical Research Council's Good Clinical Practice (MRC GCP) principles and guidelines, the Declaration of Helsinki,[35] OCTRU standard operating procedures, relevant UK/Australian/New Zealand legislation, and this protocol. GCP-trained personnel will conduct the trial.

The day-to-day management of the trial will be the responsibility of the trial manager, supported by the OCTRU administrative staff. This will be overseen by the trial management group, who will meet monthly to assess progress. 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 information specialist will be closely involved in setting up data capture systems, design of databases, and clinical reporting forms. A TSC and DSMC will be set up.

The 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 perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that

data by treatment group, and they 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.

Quality control

This study will be coordinated by the UKCRC registered trials unit (OCTRU at the University of Oxford). We will institute a rigorous programme of quality control. 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 the central trial team to ensure the integrity of randomization, study entry procedures, and data collection. The clinical trials unit (CTU) 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 consent-taking, randomization, registration, provision of information, and provision of treatment will be monitored by the central trial team. 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 regulation,s and standard operating procedures.

Patient and public involvement

Patients and children were involved from the inception of the trial, including in the development of the funding application. During the funding stage, patient representatives were involved in deciding what outcomes to collect, when to collect them, and the change required to determine superiority. The study was also discussed in detail with members of the NIHR YPAG who drafted a logo, and chose the final logo for the study through online design competition. An ongoing commitment has been made to continue to work with this group in the production of patient-facing materials and the study dissemination plan.

To ensure ongoing patient and public involvement, a patient/carer representative will be actively involved in the trial management. In addition, a further independent patient/carer representative will become a member of the steering committee.

Ethics and dissemination

In the UK, a National Research Ethic Committee approved this study on 25 March 2019 with reference number 19/NW/0158. In Australia, ethics was approved on 29 April 2021 (Reference 68948). In New Zealand, the study was approved on 30 September 2021 (Reference 21/NTB/161).

A manuscript for a high-impact peer-reviewed general medical journal will be prepared simultaneously with reports to the funder. The dissemination strategy will target the orthopaedic and emergency medicine community, the wider medical community, the National Institute for Health and Care Excellence, and policymakers. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines, and other contributors will be acknowledged. The results of this trial will substantially inform clinical practice on the clinical and cost-effectiveness of the treatment of this injury. The results of this project will be disseminated to patients via a targeted website, which includes patient explainer videos, patient information leaflets, and a clinical protocol for clinicians.

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Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

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Ethical review statement

The SCIENCE study has been reviewed by ethical boards in the UK, Australia and New Zealand. UK Ethics Reference: 19/NW/0158A. Australia Ethics Reference: 68948. New Zealand Ethics Reference: 21/NTB/161.

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Trial registration number

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