Trial Protocol

Protocol title: External frame versus internal locking plate for articular pilon fracture fixation in adult patients - a multi-centre randomised controlled trial

Short title: Articular pilon fracture trial (ACTIVE)

Trial registration: ACTIVE will be registered on International Standard Randomised Controlled Trial Number (ISRCTN98152560)

Protocol date and version number: Version 4.0 8th September 2021

IRAS Project I.D.: 224065

Ethics Reference Number: 18/YH/0014

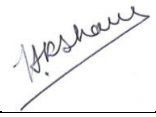
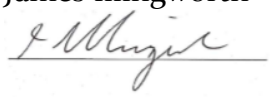
Funder: The National Institute for Health Research Health Technology Assessment programme (reference number: 15/130/84)

Sponsor: Hull and East Yorkshire Hospitals NHS Trust

Sponsor reference number: R2177

Chief Investigator: Mr Hemant Kumar Sharma, Hull and East Yorkshire Hospitals NHS Trust

Authorised by:

Name:	Mr Hemant K. Sharma	Role:	**Chief Investigator**
Signature:		Date:	13/09/2021
Name:	James Illingworth	Role:	**Sponsor Representative**
Signature:		Date:	13/10/2021

Contents

Key trial contacts

Chief Investigator	Prof Hemant Kumar Sharma Department of Trauma and Orthopaedics, Hull and East Yorkshire NHS Hospitals Trust, Hull Royal Infirmary, Analby Road, Hull, HU3 2JZ Email: hemant.sharma5@nhs.net Telephone: 01482674157 Fax: 01482 674121	
Sponsor	Hull and East Yorkshire Hospitals NHS Trust James Illingworth R&D Manager Research and Development Department Hull and East Yorkshire Hospitals NHS Trust Office 14, 2nd Floor Daisy Building Castle Hill Hospital, Cottingham HU16 5JQ Telephone: 01482 461903 Email: james.illingworth3@nhs.net Fax: 01482 461886	
Trial Coordinators		Dr Debbie Sykes York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: debbie.sykes@york.ac.uk Telephone: 01904 321083
	Miss Lydia Flett York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: lydia.flett@york.ac.uk Telephone: 01904 321283	Dr Grace O'Carroll York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: grace.ocarroll@york.ac.uk Telephone: 01904 321337
Statistician	Miss Ada Keding York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: ada.keding@york.ac.uk	Mr Alex Mitchell York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: alex.mitchell@york.ac.uk
Health Economist	Mrs Belen Corbacho York Trials Unit Department of Health Sciences Faculty of Sciences	

	ARRC Building University of York Heslington YO10 5DD Email: belen.corbacho@york.ac.uk	
Qualitative Researcher	Dr Arabella Scantlebury York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building University of York Heslington YO10 5DD Email: arabella.scantlebury@york.ac.uk	
Data manager (software development)	Matthew Bailey York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building, Lower Ground Floor University of York Heslington YO10 5DD Email: matthew.bailey@york.ac.uk Tel: 01904 321364 Fax: 01904 321387	
Data manager	Val Wadsworth York Trials Unit Department of Health Sciences Faculty of Sciences ARRC Building, Lower Ground Floor University of York Heslington YO10 5DD Email: val.wadsworth@york.ac.uk Tel: 01904 32 1363 Fax: 01904 321387	
Trial oversight committees	**Trial Steering committee:** ***Chair:*** Prof Cindy Cooper Clinical Trials Research Unit, ScHARR, The University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Telephone: 0114 22 20743 Email: c.l.cooper@sheffield.ac.uk	**Data Monitoring and Ethics Committee:** ***Chair:*** Prof. Chris Rogers Bristol Trials Centre (CTEU), Bristol Medical School, University of Bristol, Level 7, Zone A, Bristol Royal Infirmary, Bristol, BS2 8HW Telephone: 0117 342 2507 Email: chris.rogers@bristol.ac.uk
	Trial Management Group ***Chair:*** Prof Hemant Kumar Sharma Department of Trauma and Orthopaedics, Hull and East Yorkshire NHS Hospitals Trust, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ Email: hemant.sharma5@nhs.net Telephone: 01482674157	

Synopsis

<table>
<tr><td>Scientific Title</td><td colspan="2">External frame versus internal locking plate for articular pilon fracture fixation: a multi-centre randomised controlled trial</td></tr>
<tr><td>Public title</td><td colspan="2">Articular pilon fracture trial (ACTIVE)</td></tr>
<tr><td>Countries of recruitment</td><td colspan="2">England, Scotland, Wales and Northern Ireland</td></tr>
<tr><td>Health condition studied</td><td colspan="2">Closed pilon fracture of the tibia, classified AO 43- C</td></tr>
<tr><td>Interventions</td><td>Arm 1: Internal fixation: 'Locking' plate fixation with screws</td><td>Arm 2: External frame fixation: Limited open reduction and articular fixation using screws & fine wire fixator</td></tr>
<tr><td>Key Inclusion and Exclusion Criteria</td><td colspan="2">INCLUSION CRITERIA:
• Patients aged 16 years or older;
• With closed pilon fractures, classified AO 43- C which can be bi-lateral and patients with polytrauma;
• Where the treating surgeon believes the patient will benefit from surgical fixation.

EXCLUSION CRITERIA:
• Prior failed fixation;
• Pathologic fracture;
• Patient is/would be unable to understand instructions for treatment
• More than 21 days since injury
• Pre-existing (pre-injury) skin condition which precludes open surgery</td></tr>
<tr><td>Trial Design</td><td colspan="2">Parallel randomised controlled trial, with an internal pilot</td></tr>
<tr><td>Trial Participants</td><td colspan="2">Aged 16 years and older</td></tr>
<tr><td>Planned Sample Size</td><td colspan="2">334 (or revised target of 250)</td></tr>
<tr><td>Follow up duration</td><td colspan="2">3, 6, 12 and 24 months</td></tr>
<tr><td>Planned Trial Period</td><td colspan="2">1 September 2017 to 30th April 2025 (target date of first enrolment 01/03/2018)</td></tr>
<tr><td rowspan="2">Outcomes</td><td>Primary</td><td>Secondary</td></tr>
<tr><td>Disability Rating Index (DRI) at 12 months</td><td>Olerud-Molander Ankle Score (OMAS); DRI; Health related quality of life (EQ5D-5L); Complications (including non-union); Resource use (e.g. impact on the NHS and productivity).</td></tr>
</table>

Abbreviations

AE	Adverse event
CEAS	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMEC	Data Monitoring and Ethics Committee
DRAFFT	UK DRAFFT: a randomised controlled trial of percutaneous fixation with Kirschner wires versus volar locking-plate fixation in the treatment of adult patients with a dorsally displaced fracture of the distal radius
DRI	Disability Rating Index
EQ5D-5L	EuroQol 5 Dimension, 5-Level scale
ExFIX	External Fixation
FixDT	UK FixDT: Fixation of Distal Tibia fractures
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICER	Incremental Cost Effectiveness Ratio
IP	Intellectual Property
IRAS	Integrated Research Application System
ITT	Intention To Treat
OMAS	Olerud and Molander Ankle Score
MTCs	Major Trauma Centres
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
ORIF	Open Reduction and Internal Fixation
PI	Principal Investigator
PIC	Participant Identification Centre (for a study)

PIL	Participant/ Patient Information Leaflet
ProFHER	The ProFHER (PROximal Fracture of the Humerus: Evaluation by Randomisation) trial – a pragmatic multicentre randomised controlled trial evaluating the clinical effectiveness and cost-effectiveness of surgical compared with non-surgical treatment for proximal fracture of the humerus in adults
PSSP	Personal Social Services Perspective
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
YTU	York Trials Unit

1. Background and rationale

A pilon fracture is a severe ankle joint injury to the weight bearing joint surface of the bottom end of the tibia. It is caused by high energy trauma, typically in men of working age (30s to 40s) as a result of a fall from a height or traffic accident [1, 2]. Although pilon fractures are relatively uncommon, 5-7% of all tibial fractures [3-5], the risk of serious complications and long-term disability is high [2, 6].

The force required to create the fracture can lead to complex fracture configurations and extensive soft tissue damage that challenge repair [7]. This is particularly the case for complete articular fractures (Type C). Here, complications are common, and include deep infection, osteomyelitis (infection of the bone), repeat unplanned surgery including arthrodesis (permanently fixing a joint in one position), and amputation with the resultant impact on quality of life [8]. Complications can result in readmission rates of up to 50% [7, 9, 10]. Posttraumatic arthritis also occurs in a high proportion of patients even with adequate restoration of the joint [11]. Treatment is lengthy and costly. People with this injury have among the worst functional and health outcomes for any skeletal injury and it can have persistent and devastating consequences on patients' health and financial prospects [11-14].

Type C pilon fractures are managed surgically using either external fixation or internal fixation. External fixation uses a fine wire frame and pins. Once the fracture is healed, the external fixation is removed. It is often reserved for the most severe fractures, requires specialised training and is often performed in specialist centres. Internal fixation uses a plate and screws to stabilise the fracture and is performed more widely. Fine wire fixation can have a longer procedure time than internal fixation and once fixed can be very inconvenient to patients. One third of patients with external wires and pins develop infection. Although fine wire fixation is associated with a high superficial infection rate, it may lead to less deep infection, amputation and secondary intervention rate [15].

The current choice of treatment is dependent on the surgeons' training, expertise and preferences for a particular treatment. Reviews of the literature have consistently highlighted the need for high quality research, particularly randomised controlled trials (RCTs), to assess whether internal or external fixation is better for definitive management of these injuries [2, 15, 16].

Recent NICE guidance has identified the need to establish whether internal or external fixation is more clinical and cost effective for treating pilon fractures as a high-priority research recommendation [15]. They highlight this to be of high importance to both patients and to society, due to the high risk of early complications and long-term disability. As a national priority question, this research has the potential to impact on the NHS and future NICE guidance [15]. In addition the Orthopaedic Trauma Society undertook a Delphi exercise among 217 consultant orthopaedic surgeons to identify high-priority research questions in orthopaedic surgery [17]. They ranked the need to establish whether internal fixation or external circular frame fixation produces the best outcomes in pilon fractures as the 4th most important research question. Whilst the top three questions have since been addressed, the one regarding fixation remains unanswered.

It has been suggested that the cost of a single use external ring fixator is £2,500, and the cost of a plate with eight screws for internal fixation is £475, [15] though current costs are likely to be higher. While the external fixator is much more expensive than internal fixation, there may be an increased risk of deep infection with internal fixation, which can add significant costs. Direct costs of readmission for failed treatment are between £18,335 and £30,000 and can take four times longer than successful treatment [18-21]. These estimates do not take into account hospital and infrastructure costs, the wider personal and societal costs of morbidity and loss of earnings for the individual nor long-term health burden. If the lower limb is amputated, the costs of initial hospital care, rehabilitation, ongoing support and lifetime use of prosthetics can exceed £320,000 [22]. The implications of such an injury can also lead to financial hardship for the patient: only 28% of patients return to work within 20 months, and 75% report that the injury caused them financial difficulties [23].

A wide range of treatments have been described in the literature, however the standard treatments employed in the NHS for Type C pilon fractures involve either the use of internal fixation or external fixation devices [8]. There is limited evidence in the literature comparing the relative effectiveness of these treatments and that which exists is of poor quality.

NICE undertook a systematic review to establish whether fine wire external fixation is more clinically and cost effective than internal fixation for pilon fractures [15]. No economic evaluations were identified. Two RCTs and one observational study were identified [24-26]. The findings of the two RCTs indicate that internal fixation compared with external fixation may increase osteomyelitis occurrence. One RCT also showed a clinically significant increase in the number of unplanned surgeries, an increase in incidence of wound breakdown and an

increase in incidence of amputation with internal compared with external fixation. The observational study showed that internal fixation was associated with a clinically important higher health-related quality of life compared with external fixation. The quality of the evidence for all the studies was graded as either very low or low. Sample sizes were also small, between 45-60 pilon fractures, meaning that estimates of effect were very imprecise. NICE recommended that research was needed to determine whether internal or external fixation provided the best clinical and cost-effectiveness outcomes [15].

In order to address the evidence gap we will undertake an RCT and economic evaluation to establish whether internal or external fixation is more clinical and cost effective for the management of Type C pilon fractures. The outcome will directly influence clinical decision-making and health policy by informing national guidance, improve outcomes for patients and reduce the financial burden associated with the injury, as well as reduce NHS and wider social care costs.

The injury's rarity means that the involvement of the maximum numbers of centres possible who treat pilon fractures, a high rate of identification of eligible patients, and achieving a high recruitment rate are critical. We will therefore undertake an internal pilot and qualitative study in order to confirm feasibility of the main trial and ensure that trial processes are optimised before proceeding to the full trial. Given that two intensive surgical interventions are being compared we anticipate a higher recruitment rate than would be expected in a study comparing surgery to a non-surgical alternative. Previous orthopaedic trials comparing two surgical interventions have achieved high recruitment rates of around 70%, for example the DRAFTT trial [27]. However, our PPI work suggests that, although both of the interventions are surgical, patients may have strong preferences for receiving either treatment. Non-participation in a previous surgical trial was found to be associated with a concern about receiving a treatment chosen by chance and having a strong preference for a particular treatment [28]. This has been supported by other studies [29, 30]. Surgeons may also have preferences which may subtly influence how they discuss trial participation with patients [31]. These preference issues are not insurmountable but need to be carefully addressed; hence our integrated qualitative recruitment study.

2. Aims and objectives

2.1. Aim

To investigate the clinical and cost-effectiveness of internal plate fixation versus external fine wire fixation for the management of Type C closed pilon fractures of the distal tibia.

2.2. Objectives

Our objectives are to:

1. Undertake a 12 month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility

2. Explore barriers and facilitators to recruitment during the pilot phase in order to optimise trial procedures and recruitment rates

3. Undertake a parallel group multi-centre randomised controlled trial (RCT) to assess the effectiveness of external fixation versus internal fixation for Type C pilon fractures. The primary outcome is patient function at 12 month follow-up, assessed by the patient-reported outcome measure, the Disability Rating Index

4. Undertake an economic evaluation to compare the cost-effectiveness of external fixation compared to internal fixation to determine the most efficient provision of future care and to describe the resource impact on the NHS for the two treatment options

3. Trial design

The proposed study will be a multi-centre, randomised controlled superiority trial with parallel groups. An internal pilot phase, with an associated qualitative study, will assess the assumptions about recruitment and provide guidance on optimising the trial processes. A report will be provided to the funder and subject to approval from the funder (assuming feasibility has been established) we will proceed to the main trial.

4. Methods

4.1. Setting

Patients will be recruited from NHS hospitals.

4.2. Eligibility criteria

We will include all adult patients (16 years or older) with type C fractures who meet the eligibility criteria below.

4.2.1. Inclusion criteria

- Patients aged 16 years or older
- With a closed intraarticular pilon fracture of the distal tibia classified according to AO: AO 43 – C1, C2 and C3 (complete articular). This includes patients with a bi-lateral pilon fracture and who have polytrauma.
- Where the treating surgeon believes the patient will benefit from surgical fixation

4.2.2. Exclusion criteria

- More than 21 days since injury
- Previous failed fixation
- Pathologic fracture
- Pre-existing (pre-injury) skin condition which precludes open surgery
- Patient is/would be unable to understand instructions for treatment

4.3. Interventions

Eligible and consenting patients will be randomly allocated to either internal fixation or external fixation. Surgeons at each recruitment centre skilled in either or both internal and external fixation will perform the surgery according to the patient's random assignment.

4.3.1. Internal fixation

The 'locking' plate is inserted at the distal end of the tibia and passed under the skin on the surface of the bone. The details of the reduction technique, the surgical approach, the type and position of the plate, the number and configuration of fixed-angle screws and any supplementary device or technique will be left to the discretion of the surgeon. The only stipulation is that fixed -angle screws must be used in at least some of the distal screw holes – this is standard practice with all distal tibia 'locking' plates.

4.3.2. External fixation

A limited minimally invasive open reduction and fixation of articular segment is undertaken. Once the articular segment is stabilized, the circular fixator is applied to the bone. Incision site, number and configuration of screws, number of rings, wires and half pins will depend on the fracture configuration and will be left at the discretion of the surgeon. Occasionally, synthetic / iliac crest bone grafts may be necessary and circular fixator will have to extend across the ankle, which again will be left at the discretion of surgeon.

4.3.3. Routine physiotherapy advice

We will ensure that all patients randomised into the two groups will receive standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. Patients in both groups will be advised to move their toes, ankle and knee joints fully within the limits of their comfort. Early weight-bearing will be encouraged, but the details of weight-bearing status will be decided by the treating surgeon. In this pragmatic trial, any other rehabilitation input including and beyond written physiotherapy advice (such as formal referral to physiotherapy) will be left to the discretion of the treating clinicians. However, a record of any additional rehabilitation input (type of input and number of additional appointments, such as hydrotherapy) together with any other required investigations/interventions will be self-reported by trial participants as part of the 3, 6 month, 12 month and 24 month follow ups. In addition, detailed data on physiotherapy will be collected from physiotherapists using a specific CRF at the Major Trauma Centres and a sample of local referring hospitals.

4.4. Outcomes

4.4.1. Primary outcome

The primary outcome is the Disability Rating Index (DRI) at 12 months post-randomisation. The DRI is a validated patient-reported outcome measure questionnaire [32]. It consists of a 12-item

Visual Analogue Scale questionnaire assessing the patients' own rating of their disability specifically related to the lower limb. This data will be collected at baseline, 3, 6, 12 and 24 months follow-up post-randomisation. The DRI has been proven to be a robust, practical clinical and research instrument with good responsiveness and acceptability for assessment of disability caused by impairment in the lower limb. Baseline assessment will ask participants about their functioning *before* their injury and *before* their surgery.

4.4.2. Secondary outcomes

1. ***Olerud and Molander Ankle Score (OMAS):*** The OMAS is an established validated nine-item, patient-reported outcome measure developed and validated for use in clinical trials assessing symptoms following ankle fracture [35]. It contains nine items: pain, stiffness, swelling, stair climbing, running, jumping, squatting, supports and work/activities of daily living. Item responses are each scored from 0 to 25, with 0 representing the most severe state. The scale scores representing each dimension are produced by summing the responses to each item within that dimension. Raw scale scores are then converted to a metric (0-100; 0=most severe) [35]. The OMAS will be collected once at baseline (patients will be asked to complete it thinking about the week before ankle fracture) and then at 3, 6, 12 and 24 months follow-up.
2. ***EuroQol 5 Dimensions (5L) Score (EQ5D-5L):*** The EQ-5D-5L measures health-related quality of life in terms of 5 dimensions: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, anxiety and depression. Each dimension has five possible responses (no problems, slightly problems, moderate problems, severe problems and unable or extreme problems). The EQ-5D-5L will be scored according to the User Guide [36]. EQ-5D-5L data will be collected twice at baseline: *i.e.* once to assess patient health related quality of life on the day (after the injury) and once with regard to patient health related quality of life during the week before injury; then once each at 3, 6, 12 and 24 months. At baseline, the EQ-5D-5L will be collected before randomisation by patients who have capacity to consent at that time; or at the earliest opportunity after randomisation, by patients who consent having regained capacity.
3. ***Complications:*** Data on all further surgical procedures and other complications, e.g. deep wound infection (using Centres for Disease Control and Prevention definition), superficial infection, pin site infection (defined using the 'Good, Bad and Ugly' pin site grading system [37]), rehospitalisation, blood clots, wound dehiscence, septic arthritis, secondary interventions for non-union and all other secondary procedures will be

collected by Research Nurses using CRFs for infections and hospital records at 3, 6, 12 and 24 months.

3.1. Non-union, mal-union and secondary arthritis. Non-union will be defined as inability to heal as confirmed on x rays / CT scan or as secondary intervention for failure to heal. Mal-union is defined by a standard measurement based on Dror Paley's technique, undertaken using final radiographs at 12 months. Secondary arthritis in the ankle will be assessed using the Kellgren and Laurence scale [38].

3.2. To undertake these assessments we will use routine standard radiographs (anterior-posterior and lateral tibia views, with a focus on the ankle for the latter view) and/or when necessary a CT scan of the tibia, fibula and/or ankle, which will be taken at 12 months after the injury. Assessment of imaging will be undertaken by the treating surgeon at the participating site using a proforma which will then be returned to the coordinating centre.

4. ***Resource use and work impact:*** Data on resource use and work impact will be collected to inform the economic evaluation (e.g. length of hospital stay, rehospitalisation and return to work). This data will be gathered through a brief questionnaire administered to patients at 3, 6, 12 and 24 months and hospital records. Table 1 outlines the schedule of events.
5. ***Patient preference for treatment:*** Data on patient preferences will be collected as part of the patient-completed questionnaire to inform the primary statistical analysis model. Patients will be asked about their preferred treatment; and to state if they have no treatment preference at the baseline and 12 month follow-up questionnaire. At 12 month follow-up patients would be asked to state their preference by imagining if they had the same injury again.
6. ***Transition question:*** To assist interpretation of findings, patients will be asked at the 12-month follow-up time-point whether compared with when they initially sustained the pilon fracture one year previously, how their ankle is currently. This will help us to describe clinically important changes for patients, should we identify a difference between the two treatment groups.
7. ***Free text comments:*** Patients will be given the opportunity to highlight any additional issues relevant to their ankle and its impact on their daily activities at the 3, 6, 12 and 24 month time-points.

In Table 1 we outline the schedule of events for ACTIVE.

Table 1: ACTIVE Schedule of events

Time-point	Baseline	3 month follow-up	6 month follow-up	12 month follow-up	24 month follow-up
PROMS					
Disability Rating Index	X	X	X	X	X
EQ-5D – 5L	X	X	X	X	X
OMAS	X	X	X	X	X
Patient demographics	X				
Resource use		X	X	X	X
Rehabilitation (type/no. of appointments)		X	X	X	X
Return to work/normal activities		X	X	X	X
Free text comments		X	X	X	X
Patient preference for treatment	X			X	
Transition question (Compared with 1 year ago?)				X	

4.5. Sample size

The primary outcome is the DRI. In order to detect a minimum clinically important difference of 8 points on the DRI (SD 20) [32, 39, 40] with 90% power and 5% statistical significance, 133 participants per group are required (calculated using nQuery). Accounting for 20% attrition at the primary endpoint of one year follow-up, the total recruitment target is 334 participants (167 per arm). Not all participants will be followed up at the 24 month time-point. Assuming two thirds of patients included in the primary analysis are followed up to two years, statistical power will be 75% for the group comparison at two years.

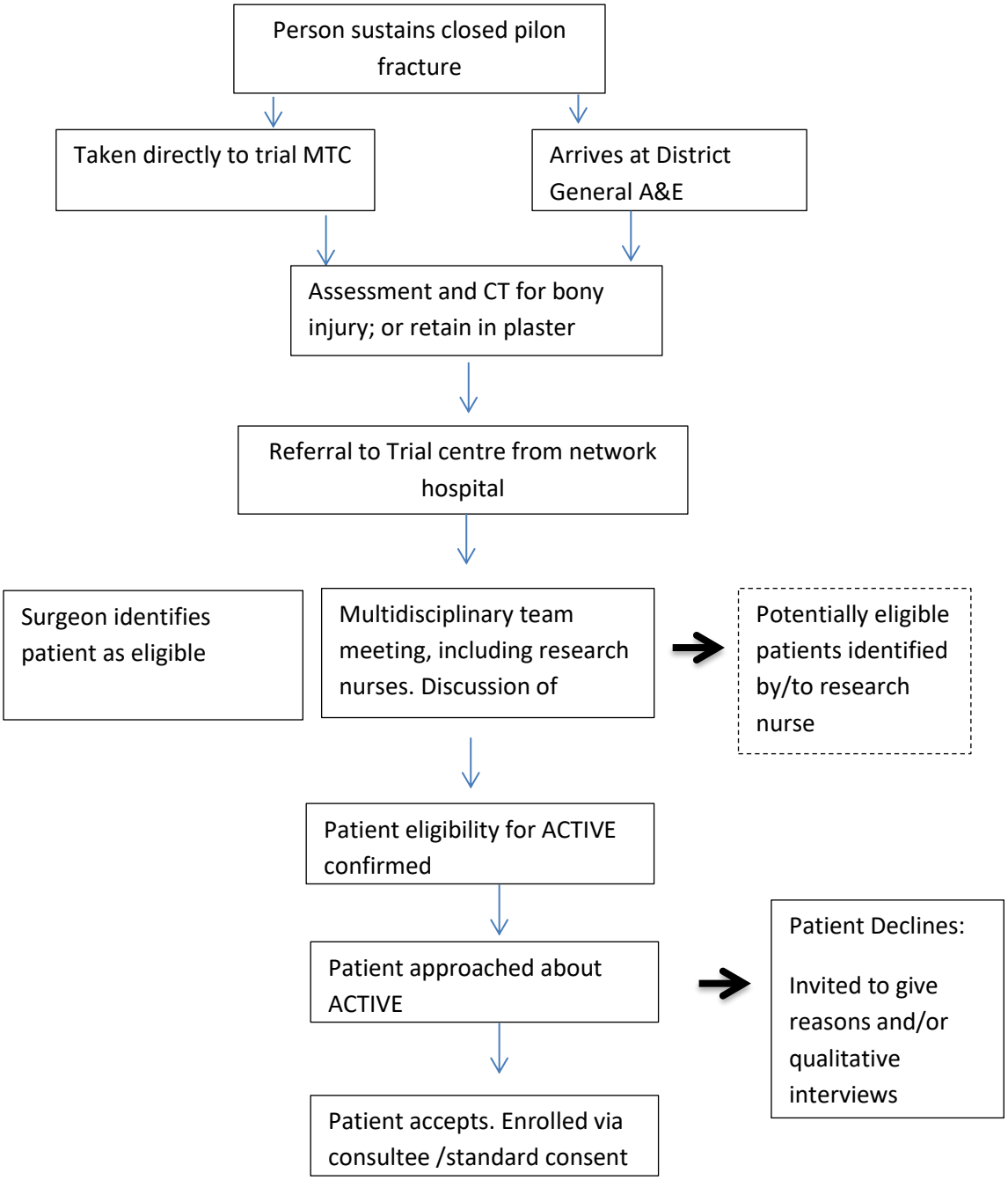
On 6th September 2021, the funder approved a request from the study team for a costed extension, with the proviso that the sample size be recalculated to provide 80% power. In order to detect a minimum clinically important difference of 8 points on the DRI (SD 20) with 80% power and 5% statistical significance, 100 participants per group are required. Accounting for 20% attrition at the primary endpoint of one year follow-up, the total recruitment target is 250 participants (125 per arm). An implication of the costed extension is that a higher proportion of patients will be followed up at the 24 month time-point. Assuming 80% of patients included in

the primary analysis model are followed up for the revised target, statistical power will be 71% for the group comparison at two years. Recruitment will continue beyond the target of 250 patients if that is met until the end of the recruitment period on 31st October 2023.

4.6. Participant recruitment

Figure 1 outlines the pilon fracture treatment flowchart and how it fits into our recruitment plans for the trial. Potentially eligible patients will be recruited from orthopaedic trauma clinics or wards, intensive care units and the emergency departments. The research team will work closely with the direct care team at each centre to optimise the screening (i.e. identification of potential participants) and recruitment for their local circumstances. A member of the patient's direct care team will first approach the patient about the study. Then the research nurse/associate will provide information about the study including an information sheet. An additional leaflet will also be available to patients who may want to know more about their pilon fracture, the treatment and possible recovery. Patients will have the opportunity to ask questions of the surgeon and the local research team. Consent will be sought for follow-up beyond the duration of the trial to allow the possibility of future long-term follow-up.

Figure 1: Pilon fracture treatment flowchart



4.6.1. Recruitment strategy

Our recruitment strategy will prioritise setting up MTCs during the recruitment phase of the trial. As part of our internal pilot phase we will pilot setting up Patient Identification Centres (PIC) for the Hull MTC site, which will involve setting up Hull's surrounding District General Hospitals, to refer eligible patients to Hull to enable them to be recruited into the trial. If this is found to be a feasible method of recruitment, we will set up PICs for other MTCs involved in ACTIVE. We will also provide MTCs with a letter to publicise the trial to referring hospitals. This is to manage treatment expectations of patients before their referral to the MTC and to encourage the continued referral of patients through the normal care pathway. Regional Trauma Networks will communicate to all Emergency Departments about the trial to encourage the referral of patients through the normal care pathway. A grid will also be available to sites that answers frequently asked questions that patients ask about the treatment options. We are also planning on setting up international sites to recruit patients into the trial.

Based on figures from a survey of interested MTCs, there are an estimated 384 cases per year (range 8 to 30 per centre). With 384 cases across 23 centres, this provides an average of 17 cases per centre per year, approximately 1.4 per centre per month. Based on data from other surgical trauma trials (Profher, HTA 06/404/53; FixDT, HTA 11/136/04) we have assumed that a conservative maximum of 50% will meet the trial inclusion criteria (192 cases). We have assumed a 70% recruitment rate as participants in both arms will receive a surgical intervention of similar intensity (DRAFFT, HTA 08/116/97; FixDT, HTA 11/136/04). This will provide an estimated maximum of 134 patients per year, on average 6 per site per year. Therefore if the assumptions hold our sample size of 334 should be achievable. The assumptions will be tested in the 12 month internal pilot.

4.6.2. Internal pilot

We will undertake a 12 month pilot study to test our assumptions about recruitment and confirm whether the trial is feasible. The internal pilot will be reviewed by the Data Monitoring Committee (DMEC) and the funder to determine whether the study progresses to the full trial. Recruitment data will be supplemented by a qualitative study on barriers and facilitators to recruitment and retention. The internal pilot and qualitative study will gather data to address the following questions: (i) are there a sufficient number of eligible patients identified and recruited in 12 months to make the trial viable within the proposed 36 month recruitment period; (ii) are there barriers to successful delivery and how can these be overcome.

At the end of the 12 month pilot we aim to have 15 sites set up and started recruiting, and a minimum of 65 patients recruited into the trial (on average 6 per centre per 12 month period).

We assume a staggered opening of recruitment sites over the 12 month pilot period (7 sites within the first 6 months and 8 further sites by month 12 of the pilot). Assuming 1.4 cases per site per month will result in 185 cases, if 50% of cases meet the trial inclusion criteria this provides an estimated pool of 93 eligible patients across 15 centres. We aim to recruit 70% giving a sample of 65.

If the assumptions are correct (93 eligible cases), we will be able to estimate a participation rate of 60 to 70% for the full trial to within a 95% confidence interval of ±10%. This will inform discussions about the feasibility of the full trial.

4.7. Randomisation

Randomisation will be undertaken by York Trials Unit. When patients have consented and their baseline forms have been completed, the recruiting research associate/nurse/clinician will contact York Trials Unit (YTU), either by telephone or via the internet, to access a secure randomisation service. The randomisation service will record information and check patient eligibility to avoid inappropriate entry of patients into the trial. When a patient has a pilon fracture in both ankles, a specific ankle will be chosen prior to randomisation at the treating surgeon's discretion. YTU will then perform independent random allocation in a 1:1 ratio to internal fixation or external fixation, using computer generated random permuted blocks of random sizes, stratified by centre.

4.7.1. Allocation concealment and blinding

Patients and treating clinicians will be informed of the allocation. Web- or telephone-based randomisation will ensure concealment of the allocation sequence. However, as with many surgical trials, where the surgical site is clearly visible, it is not feasible to blind patients, surgeons or outcome assessors to their allocation. The primary outcome is a patient-reported measure. Outcome bias will also be mitigated somewhat by both groups of patients receiving routinely available surgical treatments. We will also collect data on patient and surgeon preferences; for patients we will also ask those who do not consent for their preferences for treatment. We will account for whether patients received their preferred treatment in a secondary analysis. Staff analysing questionnaire responses will be blind to patients' treatment allocation. All recruiting centres will have surgeons who are familiar with the two techniques and perform them as part of routine NHS care.

4.8. Data collection methods

Data will be collected at recruiting sites or by post from patients, then returned to YTU for scanning and processing. All reporting of data collection will be undertaken in line with the Consolidated Standards of Reporting Trials (CONSORT) statement. Data will be collected at baseline, 3, 6, 12 and 24 months post-randomisation.

4.8.1. Internal pilot data collection

Screening logs will be kept by participating centres throughout the trial. We will collect data on: number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent and reasons why; proportion of patients providing consent who are randomised. We will also collect data on the proportion of patients randomised who do not receive the randomly allocated treatment and reasons why. Additionally, we will collect data on numbers of patients recruited with C1, C2 and C3 subtypes. Experience in either surgical procedure will be collected from all surgeons, including the predominant procedure used for their patients. During site set up, the training delivered to sites will cover equipoise. The assumption of surgeon equipoise will be monitored during recruitment by scanning reasons for exclusion during screening and reasons for crossover following randomisation that may reflect surgeon preferences. This data will inform whether the study progresses from internal pilot to full study and will be used throughout the trial to monitor progress and identify potential areas to target to improve recruitment rates.

4.9. Follow up

Participants will be followed up at 3, 6 and 12 months post-randomisation. The primary follow-up point is 12 months post-randomisation. We will have an additional secondary outcome endpoint of 24 month follow up for all patients recruited except for those in the last year of the recruitment period. This will enable us to gather data for the secondary outcomes and economic analysis, whilst reducing costs and total length of the trial by 12 months. All follow-up will be undertaken through postal questionnaires. Follow-up data of patient questionnaires may also be collected at 3, 6, 12 and 24 months in NHS clinics where follow-up clinics form part of routine care, as necessary. Radiographs are those routinely used for the investigation of patients with a suspected fracture of the distal tibia and for the follow-up of such patients following any intervention, so there will be no need to request any additional or special investigations.

To minimise attrition, we will use multiple methods to keep in touch with patients. Firstly, if patients need help completing the questionnaires one of the study team can help them complete them over the telephone. This includes calling the patient if there is missing data on the primary outcome when the questionnaire is returned and other missing data as feasible. We will ask patients for full contact details (including mobile phone number and email address). A pre-notification letter will be sent 2 weeks before the follow-up questionnaire is due at 3, 6, 12 and 24 months, to help prime participants and find out if they are no longer at that address. A text message reminder will also be sent on the day patients are expected to receive the postal questionnaire at 3, 6, 12 and 24 months. This has been shown to significantly reduce time to questionnaire response [41]. We will also send 2 and 4 week reminders. Where these methods fail we will give participants the option for completion of an abridged questionnaire (a minimum of the DRI and EQ-5D) via telephone or electronically after the 4 week reminder and will also contact them about this by SMS messaging. At 3, 6, and 24 month follow-up, we will include an unconditional incentive payment of £5 to maximize the completion and return of questionnaires. At 12 months this will increase to £20 to also cover expenses for attending the hospital clinic to perform imaging to assess bone healing [42]. We will also write newsletters during the trial to keep the participants informed and engaged with the trial which can enhance response rates [43].

A management system which will be used to track participant recruitment and study status as well as Case Report Form (CRF) returns. Data from CRFs will be processed by administrative personnel. Data will be verified through cross checking of the data against the hard copy of the CRF. The trial coordinator and statistician will write a Validation Plan for the CRFs in consultation with the YTU Data Manager. The Plan will include detailed coding for the CRFs and data query resolution rules/procedures. Quality Control will be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

4.9.1. Short messaging service (SMS) sub-study to minimise attrition

We will undertake an embedded randomised controlled trial to evaluate the effectiveness of sending an SMS text message reminder with the option for participants to reply to, compared with a standard text message with no option to reply on postal questionnaire response rates. Participants will be randomised in a 1:1 ratio to receive either a text message with a reply option or the York Trials Unit standard text with no reply option with their 3-month follow-up questionnaires. The wording for the text with the reply option will read *"ACTIVE Trial: you should have received a questionnaire in the post by now. Your answers are important; so please*

help by returning it as soon as you can. To get in touch with us you can reply to this message. Thanks". The wording on the standard no-reply text will read *"ACTIVE Trial: you should have received a questionnaire in the post by now. Your answers are important; so please help by returning it as soon as you can. Thanks".* Participants will be sent the text messages at the same time as they are expected to receive their postal follow-up questionnaire (i.e., two to four days after the questionnaire is sent). Text messages are likely to be sent using secure UK-based text message gateway software such as that provided by Intelli Software (https://www.intellisoftware.co.uk). In the event that a message is not delivered, the sender will receive a notification, which will be used to classify the text message as "delivered" or "not delivered". The findings of this sub-study will be implemented during the course of this study. Once the results of this sub-study become available, participants will receive the text which demonstrated the highest questionnaire response rate, at subsequent follow-up time-points.

4.10. Qualitative study involving patients and surgeons

Our 12 month pilot study will include a qualitative component to highlight any barriers or facilitators to recruitment and retention of trial participants. This will inform any improvements that can be made to the recruitment process and how the trial is communicated to potential participants in the full trial. There will be two components: (i) interviews will be conducted with patients who agree to take part in the trial (n=15-20) and who decline participation (n=5-10); (ii) interviews with participating surgeons and trial recruiters regarding their preferences and views on the trial (n=15-20). We will also seek permission from the patient and trial recruitment teams to audio-record recruitment consultations where feasible. This will be on a voluntary basis. Implicit consent will be taken from trial recruitment teams by the return of completed recordings. Recruitment teams will be asked to obtain verbal consent from patients to audio-record consultations. A selection of consultation recordings (from those declining and accepting participation) will be analysed thematically in order to identify improvements in communication regarding how best to explain randomisation and the different care pathways [44].

4.10.1. Data collection: qualitative study

We will undertake semi-structured interviews with people who agree to take part in the trial including patients from both treatment options, and those who decline participation. A flexible interview schedule will be developed following discussions with the research team, PPI

members and surgeons with expertise in this area. Interviews will be conducted face-to-face, telephone or Skype according to the preferences of each interviewee. All interviews will be recorded with permission. These interviews will explore patients' responses to the invitation to join the trial; their experiences of the trial processes; and reasons for participation/non-participation. Patient interviewees will be purposefully sampled to ensure maximum variation from the cohort of interviewees who are eligible for recruitment into the trial and will be based on age, gender and responses to the quantitative questions relating to treatment preferences and reasons for non-consent into the trial. In addition, we will carry out interviews with participating surgeons and trial recruiters from across all of the participating centres regarding their preferences and views on the trial, the barriers and facilitators to offering these interventions and willingness to randomise. We will interview participants until no further conceptual categories emerge, therefore we have provided for some flexibility in the sample size, however, this number is consistent with recommendations [45].

Interviews with patients will be conducted as soon as possible after the invitation to participate in the study to discuss in more detail the participants' experiences of making the decision to enrol/decline; trial procedures; the intervention they were given; and their recovery. We will specifically ascertain how the participants felt about the randomisation process and to provide feedback on the information they were given and what (if any) information was missing – for example, information pertaining to their immediate recovery etc.

5. Data management

Study data will be recorded in a number of files for both the administration of the study and collection of patient data. All data will be completely anonymised for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, once randomised, individual patients will only be identified by trial numbers.

For the qualitative interviews, all participants will be assigned a unique ID so as to maintain anonymity. Recordings and transcripts will be anonymised and stored on a password-protected computer for three years following completion of the study. Only the research team will have access to qualitative data. Consent forms will be kept in a locked filing cabinet, separate to the other data collected for the study. Transfer of data to any external transcriber will be via the University based secure web-based data transfer system.

5.1. Data entry

The data collected by sites using paper CRFs, will be mailed (original paper CRFs) to YTU to be entered/scanned into a secure web-based interface, specifically developed for this study. When necessary, a site can securely return the CRF electronically.

The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards.

Data will be checked according to procedures detailed in the trial specific Data Management Plan.

5.2. Data storage

Each site will hold data according to the Data Protection Act 1998 and data will be collated in CRFs identified by a unique identification number (i.e. the Trial number) only. A Trial Enrolment Log at the sites will list the ID numbers. YTU will maintain a list of trial numbers for all trial patients at each site.

All YTU data recorded electronically will be held in a secure environment with permissions for access as detailed in the delegation log. The Department of Health Sciences, in which YTU is based at the University of York, has a backup procedure approved by auditors for disaster recovery. Full data backups are performed nightly using rotational tapes, to provide five years' worth of recoverable data. The tape backup sessions are encrypted and password protected, with tapes stored in a locked fire-proof safe in a separate secured and alarmed location. All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at the YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All essential documents, including source documents, will be retained for a minimum period of five years after study completion. The separate archival of electronic data will performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements. All work will be conducted following the University of York's data protection policy which is publically available (www.york.ac.uk/records-management/dp/policy).

5.2.1. Proposed time period for retention of relevant trial documentation

Essential trial documentation will be kept with the Trial Master File and Investigator Site Files. The Sponsor will ensure that this documentation will be retained for a minimum of five years after the conclusion of the trial to comply with standards of Good Clinical Practice. Case Report

Forms will be will be stored up to 10 years after the conclusion of the trial as paper records; and a minimum of 20 years in electronic format in accordance with guidelines on Good Research Practice [46]. All paper records will be stored in a secure storage facility at York Trials Unit or in the longer term transferred to a secure off-site storage facility. All electronic records will be stored on a password protected server. For the qualitative interviews, recordings and transcripts will be anonymised and kept in a locked office for three years following the completion of the study.

5.3. Quality Assurance and Quality Control

Hull and East Yorkshire NHS Trust is the lead sponsor for this project and takes overall responsibility for the quality of study conduct. This study will be fully compliant with the Research Governance Framework and MRC Good Clinical Practice Guidance. A trial specific data management plan agreed by the Chief Investigator, Sponsor, YTU and other study investigators will be drafted to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

A rigorous programme of quality control will be undertaken. The day-to-day management of the trial will be the responsibility of the Trial Co-ordinator based at York Trials Unit. Regular meetings with the Trial Management Group will be held and the trial team will monitor adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by York Trials Unit to ensure integrity of randomisation, study entry procedures and data collection.

5.4. Statistical methods

5.4.1. Statistical Analysis Plan

Full analyses will be detailed in a statistical analysis plan (SAP), which will be finalised prior to the end of data collection and which will be reviewed and approved by the independent data monitoring committee. Any exploratory analyses of sub-groups that are of clinical interest will be pre-specified in the SAP. This trial will be reported according to the CONSORT guidelines for clinical trials (Consolidated Standards Of Reporting Trials statement).

5.4.2. Internal pilot

The recruitment rate and 95% confidence interval (CI) will be estimated from the data collected. A CONSORT diagram will be constructed to show the flow of participants through the study

and the following outcomes calculated: number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent; proportion of patients providing consent who are randomised; proportion of patients randomised who do not receive the randomly allocated treatment; proportion of patients dropping out between randomisation and follow-up. Data will be summarised on the reasons why eligible patients were not approached, reasons for patients declining to participate in the study; reasons why randomised patients did not receive their allocated treatment and reasons for drop-out, if available. Results will be compared against the study's recruitment assumptions and progression targets, and continuation of the trial or relevant modifications will be decided by the funding body.

5.4.3. Statistical analysis - main trial

A CONSORT flow diagram will be provided to display the flow of participants through the study (see Figure 2). The number of participants withdrawing from the trial will be summarised with reasons where available. Baseline characteristics will be presented by trial arm both for the trial population as randomised and for those patients for whom primary outcome data was available at 12 months follow-up. Statistical analyses will be on intention to treat (ITT) basis with patients being analysed in the groups to which they were randomised. Statistical significance will be at the 5% level, and analyses will be conducted in the latest available version of Stata or similar statistical software. All trial outcomes will be reported descriptively by trial arm at all time points at which they were collected. Continuous PROMS data will be summarised as means, standard deviations, medians and ranges, whereas data on further procedures and complications will be summarised as frequencies and percentages. Outcomes will be illustrated graphically over time where appropriate, including confidence intervals.

The primary analysis model will be a mixed effects regression analysis, with DRI scores at 3, 6 and 12 months follow-up as the dependent variable, adjusting for baseline DRI, randomised treatment arm and other pertinent baseline characteristics as fixed effects and including treating centre and surgeon as random effects. We will consider adjusting on fracture type and baseline DRI; however we will first monitor how well fracture type and baseline DRI are collected during the pilot phase to determine whether these adjustments are feasible. The model will account for similarities of scores by the same person by means of an appropriate covariance structure. The estimated treatment group differences at 12 months will be reported as the primary endpoint with 95% confidence interval and associated p-value. Secondary analyses of

the primary outcome will include an estimate of treatment group differences at 3 and 6 months from the same model. A separate model additionally including 24 month data will derive treatment group differences at that point. The overall treatment effect across all prior time points will be derived at 12 and 24 months (equivalent to area under the curve estimates).

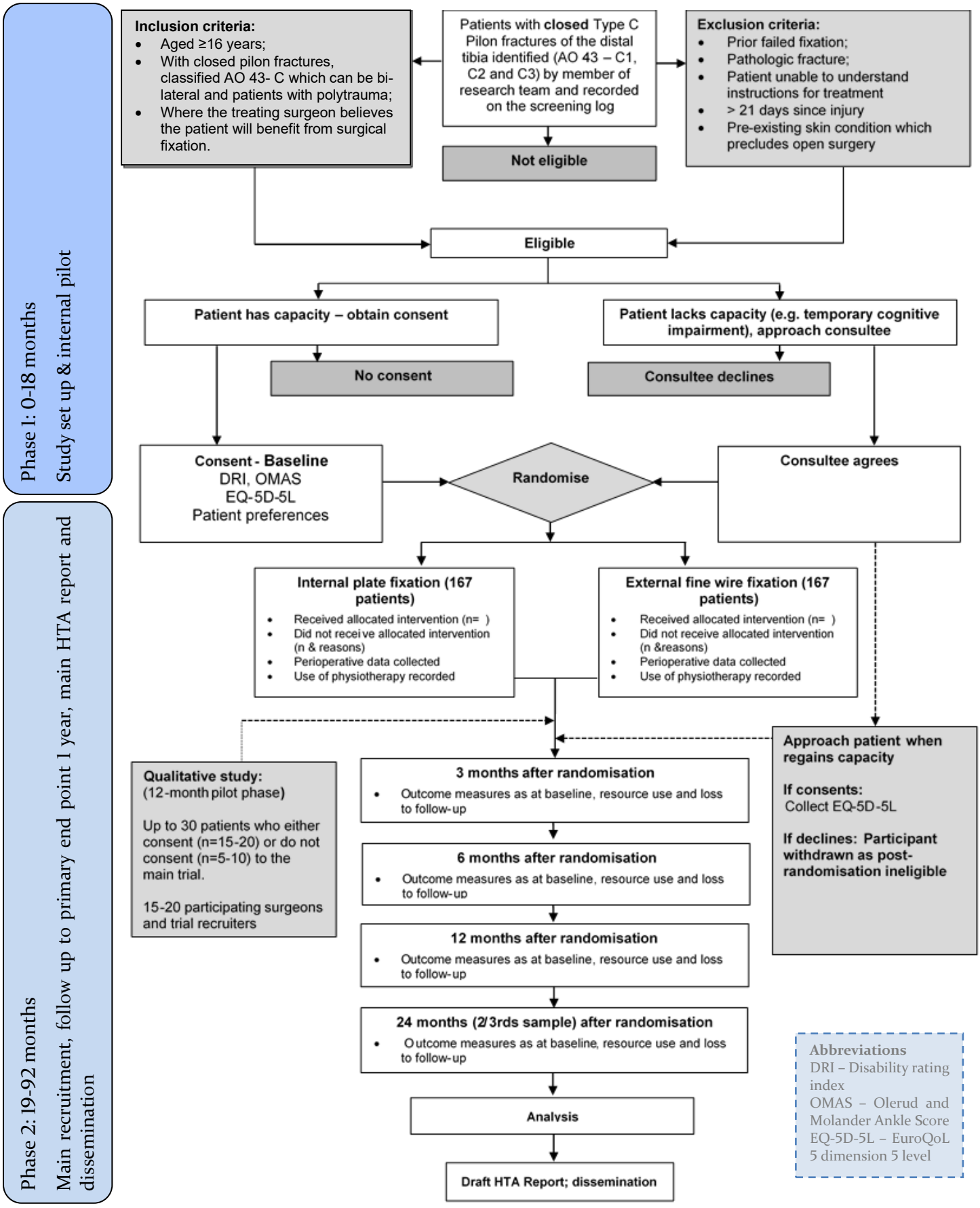
The amount of missing data will be mitigated by including 3, 6 and 12 month data in the primary analysis model, which allows the inclusion of any patient with complete baseline data and valid outcome data at one or more follow-up points. The nature of missingness for outcome data will be explored and multiple imputation and/or deviations from the missing-at-random assumption considered if appropriate.

There will be two exploratory subgroup analyses of the primary outcome, to assess the effectiveness of the different treatments across different patient subgroups. One will consider the impact of baseline patient preferences, whereby an interaction between treatment arm and patient preference (receipt of preferred treatment, non-preferred treatment, no prior preference) will be added to the primary analysis model. The other will consider fracture types (C1+C2 vs C3), whereby an interaction between treatment arm and fracture type will be added into the primary analysis model. These interactions will be presented graphically, and the p-value of the interaction will be reported. While there is insufficient statistical power for these interactions, they may help inform further research.

We will consider the impact that time to surgery has on the primary outcome by reporting DRI scores descriptively for the four patient groups formed by considering treatment allocation together with time to surgery (early (within 36 hours) Vs. late).

Secondary continuous PROMS outcomes will be analysed by similar mixed effects regression analyses to the primary analysis model. Binary secondary outcomes of additional procedures and complications will be analysed by mixed effects logistics regression analyses.

Figure 2: ACTIVE Trial CONSORT flow diagram



5.4.4. Cost-effectiveness analysis

The aim of this economic evaluation is to assess the cost-effectiveness of internal plate fixation in comparison with external fine-wire fixation for the treatment of Type C pilon fractures of the distal tibia. Therefore a cost-effectiveness analysis will be conducted as part of this trial. Costs and health outcomes associated with the surgical interventions will be collected over the follow-up period of the trial. The perspective of the analysis will be that of the National Health Services (NHS) and Personal Social Services (PSS).

The primary outcome for the economic analysis will be the additional cost per quality-adjusted life year gained of internal plate fixation compared to external fine-wire. Hence the value for money will be estimated in terms of cost per QALY following an intention-to-treat approach. Data on resource use and health outcomes will be collected prospectively during the analysis using self-reported questionnaires at baseline, 3, 6, 12 and 24 months and hospital CRFs. A discount rate will be applied to all costs and QALYs accrued after 12 months at a rate of 3.5% per annum in line with NICE guidance [47].

If the results deem appropriate (i.e. there is a non-dominant situation in the trial based evaluation) we will carry out a secondary analysis to explore how the differences observed during the trial evolve beyond the study. For this projection, we will use a decision modelling approach to extrapolate the cost-effectiveness data observed in the ACTIVE trial to a life time horizon. The analyses will be based on a combination of observed in-trial cost and HRQoL and projections of life expectancy. In the model, each patient will assume to encounter an annual risk of death based on age and sex obtained from UK life tables.

Self-reported questionnaires, including attendance at physiotherapy and hospital forms will be specifically designed to collect information on hospital stay (initial and subsequent inpatient episodes, outpatient hospital visits and A&E hospital admissions); primary care consultations (e.g. GP, nurse and physiotherapy); out-of-pocket costs and work impact of both interventions as well as return to work. The cost of each type of surgery and related complications will be essential for the analysis. Hence an accurate record of procedures at hospital level (e.g. centres in the trial) will be put in place in order to record per patient information (e.g. surgical procedures, complications related to the surgical intervention, other medical complications). Costs relating to surgical procedures will be based on time in theatre, staff time, consumables and devices, and nights in hospital after the procedure. These data will be collected via a surgical form that will be specifically designed for this trial. In order to describe the resource impact of re-operations in this clinical area, we will also collect Healthcare Resource Groups on discharge

for each admission. Similarly we will ask patients for consent to access Hospital Episode Statistics (HES) data in case it is deemed appropriate to monitor long term hospital care related to their initial injury and its treatment. Unit costs will be derived from established national costing sources such as NHS Reference Costs, PSSRU Unit costs of health and social care, and the British National Formulary. Unit costs will be multiplied by resource use to obtain a total cost for each patient. As already stated the EQ-5D-5L questionnaire will be also included in the questionnaires to measure the impact of the intervention on patient's health related quality of life. We will present descriptive statistics of the utility scores for both trial arms at each data collection point. The raw EQ-5D scores according to domain will be displayed, in order to examine the movements between levels for each domain according to the trial arm. The overall difference in EQ-5D index scores between the two arms will be examined through regression methods, consistent with the model selected in the statistical analysis. The EQ-5D health states will be valued using a UK-based social tariff. QALYs will be calculated by plotting the utility scores at each of the three time points and estimating the area under the curve [48].

For the analysis, regression methods will be used as this allows differences in prognostic variables. The pattern of missing data will be analysed and handled by means of multiple imputation (MI)[49]. A range of sensitivity analysis will be conducted to test the robustness of the results under different scenarios, including probabilistic sensitivity analysis. In case of positive results of the trial, we will recommend that costs and outcomes will be extrapolated and modelled over a longer time horizon than captured by the trial (e.g. lifetime of the patient).

Full analyses will be detailed in a Health Economic Analysis Plan (HEAP).

5.4.5. Qualitative analysis

We will use NVivo software to assist our organisation of the qualitative analysis. To achieve a systematic approach to data analysis we will engage in: detailed familiarisation; identification and indexing of key themes; contextualising these themes in relation to the broader dataset; and interpreting them with a focus on addressing the specific aims of the study:

- Are surgeons willing to randomise eligible patients and adhere to randomisation to internal or external fixation?
- What are patients' experiences of being approached to participate in the trial?
- Are patients willing to be randomised in a trial comparing the two treatments?

- What are the barriers to successful delivery of the future trial and how can they be overcome?

Initially following transcription, the interview material will be organised according to analytical headings using a constant comparison approach [50]. We will combine coding with a holistic consideration of transcripts to retain the context of participants' narratives whilst accounting for deviations. Data from consultation recordings will also be analysed thematically and integrated with interview data. During the analysis, regular meetings will be held between the research team, and PPI participants where appropriate, to discuss the emergent themes from the qualitative interviews and consultation recordings. Findings from the qualitative work will be integrated with the pilot RCT outcomes in order to inform the design of a full-scale RCT.

5.5. Data monitoring

The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial Sponsor. Data monitoring will be undertaken by the Trial Management Group (TMG), Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC), on behalf of the Sponsor and Funder. The project will also be monitored by the Sponsor for whom a representative will be invited to attend the Trial Management Group and Trial Steering Committee meetings and we will submit regular progress reports to the Funding Body.

5.5.1. Trial Management Group (TMG)

A TMG has been established to oversee the day-to-day management of ACTIVE, and is chaired by the Chief Investigator. Other members include the trial statisticians, trial manager, trial coordinators, health economist, qualitative researcher and other co-applicants. The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly by teleconference, with quarterly face-to-face meetings where feasible, from the start of the study until the end of the pilot. The TMG will meet more frequently if there is a need to monitor recruitment more closely. The TMG will then meet quarterly.

5.5.2. Trial Steering committee (TSC)

An independent TSC has been established to provide overall supervision for ACTIVE on behalf of the Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health

and Social Care and the Guidelines for Good Clinical Practice. This committee comprises of an Independent Chair who is a Professor of Health Services Research and Clinical Trials, a consultant orthopaedic surgeon with expertise in surgically fixing pilon fractures, a public contributor, the Chief Investigator and Trial Coordinator/Manager. Other study collaborators may also attend the meeting with the agreement of the Chair. The TSC will meet at least annually and will work to a Charter which has been agreed.

5.5.3. Data monitoring and ethics committee (DMEC)

The role of the DMEC is to review accumulating data in ACTIVE and advise the sponsor (directly or indirectly) on the future management of the trial. The DMEC is Chaired by a statistician, with other members comprising of experts in the clinical area. The DMEC will review safety and efficacy data as well as quality and compliance data. The DMEC will review all serious adverse events which are thought to be treatment related and unexpected. The independent members of the DMEC committee will be allowed to see unblinded data. The DMEC will meet at least annually or more frequently if the committee requests. A DMEC Charter has been agreed which they will work to.

6. Harms

6.1. Risks and anticipated benefits

In the context of the lack of robust evidence to determine the best surgical intervention for patients with these injuries, the risks are not increased through trial participation. However, there are risks associated with this study, which are predominantly the risks associated with the surgery: infection, bleeding and damage to the adjacent structures such as nerves, blood vessels and tendons. Participants in both groups will undergo surgery and will potentially be at risk from any/all of these complications.

In this trial surgeons will perform interventions which they undertake as part of routine practice and with which they are familiar. Measures taken by us, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. We will adhere to the Research Governance Framework/ UK Policy Framework for Health and Social Care Research and MRC Good Clinical Practice Guidance [51, 52] [53]. The participant information sheet for the study will be developed with the involvement of service users and will give a balanced account of the possible benefits and known risks of the

interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants after they have had sufficient time to read the study materials and ask questions. Whilst we will recruit participants who do not have capacity to consent via a professional or personal consultee, we will not recruit patients who do not have the capacity to understand the instructions for treatment. An application for NHS ethical approval will be made. We do not anticipate major ethical concerns with this study. The only potential concern would be the inclusion of patients who lack mental capacity to understand instructions for treatment. We will allow the treating clinician to exclude these patients from this trial. The local R&D committee of each of the participating hospitals will approve local involvement in the trial. The trial will be subject to DMEC and TSC oversight.

6.2. Informing potential trial participants of possible benefits and known risks

Informed consent will be obtained by the trained local research nurse or clinician using a patient information leaflet developed with the help of service users, which explains the risks and benefits clearly. In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the TSC for addition to the patient information leaflet. A revised consent form will also be completed if necessary.

6.3. Adverse event management

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial participant and which do not necessarily have a causal relationship with the treatment. We will only collect adverse event data related to treatment for the original injury, that are 'unexpected' and only up until the 24 month follow up. All AEs will be listed on the appropriate Case Report Form for routine return to York Trials Unit. Serious adverse events are defined as any untoward and unexpected medical occurrence that: 1) Results in death; 2) Is life-threatening; 3) Requires hospitalisation or prolongation of existing inpatients' hospitalisation; 4) Results in persistent or significant disability or incapacity; 5) Is a congenital anomaly or birth defect; 6) Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed. A list of expected adverse events that we will not report is given in Table 2. This is because these are well known complications

that will be recorded on other CRFs for the two routine surgical treatments that the specialist clinical care teams will be experienced in managing.

Table 2: Expected adverse events

Wound complications (e.g. delayed healing)
Infection at the surgical site or adjacent joint
Pin site infection requiring procedure, antibiotics or admission
Damage to a nerve or blood vessel
Breakage of orthopaedic hardware
Thromboembolic events
Secondary operations for or to prevent infection, malunion, non-union or for symptoms related to the metalwork.
Wire breakage and removal / exchange of wire
Partial / complete frame removal
Chronic Regional Pain Syndrome
Amputation
Elective admissions to hospital for the ankle
Abnormal blood results related to an infection

All serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and faxed to a dedicated fax machine at York Trials Unit within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings. Follow up reports a month later will be reviewed by the CI to ensure that adequate action has been taken and progress made.

7. Research ethics approval

As the study is led from England, an application for NHS ethical approval in England will be made and we will also apply to the Health Research Authority (HRA) for governance approval. Local R&D will confirm the capacity and capability of centres to participate. We do not anticipate major ethical concerns with this study. The only potential concern would be the inclusion of patients who lack mental capacity to understand the trial treatment. We will allow the treating clinician to exclude these patients from this trial.

7.1. Protocol amendments

Any amendments to the protocol during the course of the trial will be submitted for approval by the REC/HRA as necessary.

Responsibility for recording and dating both oral and written informed consent or agreement will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log.

7.2. Consent

Some patients screened for inclusion in the study may be unconscious due to trauma, all will be distracted by the injury to their leg and its implications and patients may have received large doses of pain killers, affecting their ability to absorb, retain and process information. Therefore, patients with injuries relevant to the study might lack capacity to make a decision about participation in a research project, but it would not be ethically sound to exclude this population from potential inclusion in a relevant research study focused on the condition that has affected them. We will review the number of patients who lack capacity during the internal pilot phase.

7.2.1. Consenting patients who have capacity

Research nurses or attending clinician will invite the patient to consider joining the study. They will be provided with a participant information sheet and have the opportunity to ask questions of the surgeon and the local research team.

Patients who decline to continue to take part during the feasibility phase will be given the opportunity to discuss/inform the research team of their reasoning behind their decision not to take part.

7.2.2. Consultee consent – patients who lack capacity

A proportion of patients may be unconscious or may experience head injury and therefore lack capacity to make an informed decision about their participation in the research project; or are taking opiate-based pain killers which means their mental capacity may be impaired. In these instances we will consult with a Personal or Professional Consultee in line with the Mental Capacity Act 2005. Where a personal or professional consultee has agreed on behalf of a patient to take part, we will seek formal written consent retrospectively from the patient for continuation in the trial at the earliest appropriate time once they regain capacity. A patient information leaflet and consent form will be provided for review and the patient will have the opportunity to ask questions of the study team and to discuss the study with their friends or family before reaching a decision. They will then be asked to confirm their willingness to continue in the study and indicate this by signing the study consent form. If patients do not wish to enrol in the trial after a Personal or Professional consultee has been consulted, they will be withdrawn from the trial. We planned to implement this consultee process in Scotland according to their legal frameworks; that is, the Adults with Incapacity (Scotland) Act, 2000. However, Scotland A Research Ethics Committee advised that we could not recruit patients who lack capacity to consent as according to their legislation the research is not connected with the treatment of the adult's incapacity. Northern Ireland will also not recruit patients who lack capacity to consent as it will be a rare occurrence and it's most likely the patient will receive internal fixation because of the understanding that is required of a patient when being rehabilitated with a frame. Specific consent will be sought to facilitate the sharing of identifiable data with YTU as part of the study to facilitate the collection of outcome data.

7.2.3. Documenting consent

The original signed consent form will be kept in the investigator site file. Three additional copies of the consent forms will be made; one held in the patient's medical notes, one for the patient, and one copy to be returned to YTU. The primary outcome measure in the trial is a patient reported outcome measure. Therefore participants who do not regain capacity or permanently lack capacity at 3 months following randomisation (the time of the first follow up data collection) will be withdrawn from the study. We will monitor this during the internal pilot phase. Throughout the whole study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion.

7.3. Patient confidentiality

The researchers and clinical care teams must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a Trial number and this will be used on CRFs; patients will not be identified by their name in order maintain confidentiality.

All records will be kept in locked locations. All consent forms will be secured safely in a separate compartment of a locked cabinet Clinical information will only be looked at by responsible individuals from the study team, the Sponsor, the NHS Trust, or from regulatory authorities; where it is relevant to the patient taking part in this research as he/she would have agreed to at the time of consent.

7.4. Proposed action to comply with the medicines for human use (clinical trials) regulations 2004

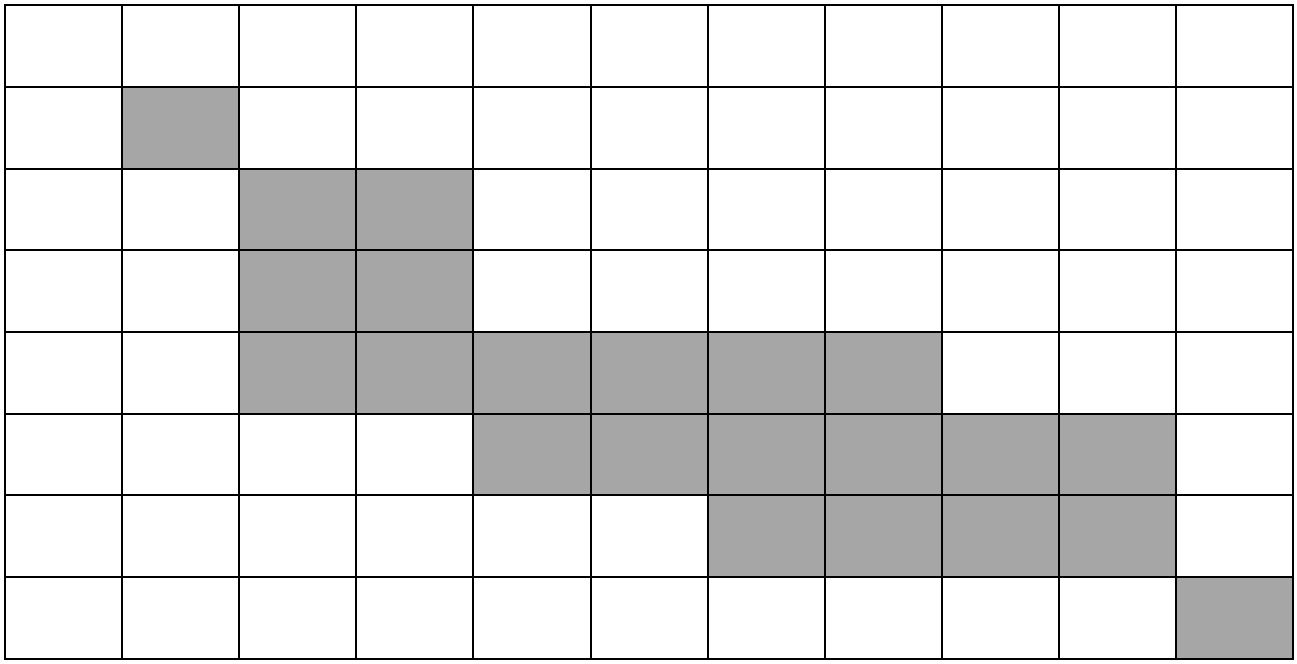
The techniques under investigation are well-recognized and international accepted surgical procedures using CE-marked implants and medical devices. We do not therefore require prior authorisation by the UK Competent Authority, the MHRA, under the Medical Devices Regulations (2002).

8. Plan of investigation and timetable

The proposed start date is 1st September 2017 with a 60 month study duration. The internal pilot will take place from months 7 to 18. With a 32 month extension to the project the study will now be 92 months in duration and end 30th April 2025. The project plan is summarised below.

	1-6	7-18	19-27	27-38	39-50	51-62	63-74	75-86	87-92
Set up									
Internal pilot									
Qualitative									
Recruitment									
12 month follow-up									

24 month follow-up										
Analysis & write up										



9. Declaration of interests

- Mr H K Sharma: Paid Consultant for Orthofix, Biocomposites and Smith & Nephew. Research Grants from Smith & Nephew, BBraun, Dermol Laboratories and Orthofix.
- Mr Nikolaos Giotakis: Paid Consultant for Orthofix
- Prof David Torgerson: No conflict of interest declared
- Prof Catherine Hewitt: Is a member of the NIHR HTA commissioning board
- Dr Catriona McDaid: Is a member of the NIHR HTA and EME Editorial board
- Prof Matthew Costa: Is a member of the HTA General Board
- Belen Corbacho: No conflict of interest declared
- Miss Ada Keding: No conflict of interest declared
- Prof Joy Adamson: No conflict of interest declared

- Dr Adwoa Parker: No conflict of interest declared
- Mrs Elizabeth Barron: No conflict of interest declared
- Dr Stephen Brealey: No conflict of interest declared
- Dr Arabella Scantlebury: No conflict of interest declared
- Dr Matthew Northgraves: No conflict of interest declared
- Mrs Emma Turner: No conflict of interest declared
- Dr Deborah Sykes: No conflict of interest declared
- Mr Alex Mitchell: No conflict of interest declared
- Mr Charlie Welch: No conflict of interest declared
- Miss Lydia Flett: No conflict of interest declared
- Dr Grace O'Carroll: No conflict of interest declared

10. Access to data

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the patient consent form with explicit explanation as part of the consent process and Participant Information Sheet. Once YTU has completed the analysis and published all intended scientific journals, the data will be made available for other researchers.

In principle, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and study Sponsor.

The Investigator(s)/Institutions will permit monitoring, audits, and REC review (as applicable) and provide direct access to source data and documents.

11. Indemnity

This study will be sponsored by Hull and East Yorkshire NHS Trust. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

12. Finance

The financial arrangements for the study will be as contractually agreed between the funder (HTA), the University of York and the Sponsor (HEY NHS Foundation Trust).

13. Dissemination and projected outputs

Through the planned outputs, the study is expected to play a key role in enhancing the evidence base on the effectiveness and cost-effectiveness of internal and external surgical fixation for the management of pilon fractures. The economic component will help us to identify the most efficient provision of future care and thus savings to the NHS and society. The qualitative investigation of patient experiences of the treatment options will provide important patient-centred insight to further guide clinical decision-making.

The executive summary and copy of the trial report will be sent to NICE and other relevant bodies, including Clinical Commissioning Groups, so that study findings can inform their deliberations and be translated into clinical practice nationally. We will work with the relevant Specialty Advisory Committees (SAC) to incorporate the findings into the training curriculum for clinicians who will undertake treatment for pilon fractures. We will use a number of dissemination channels to ensure that patients and the public are also informed about the results of the study. We will produce the following outputs:

- The study protocol will be published in a peer-reviewed, open access journal.
- A HTA research monograph will be produced.
- In conjunction with patient members of the team we will generate patient information for "Shared Decision Making" based on findings from this trial and update the entry on Wikipedia [54] and write the Map of Medicine [55] entry on pilon fractures management.
- The results of the study will be presented at national and international surgical meetings such as the British Orthopaedic Association Annual Congress, the UK Orthopaedic Trauma Society meeting, the North American Orthopaedic Trauma Association the European Federation of National Associations of Orthopaedics and Traumatology (EFFORT), Société Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT and the American Academy of Orthopaedic Surgeons.

- The findings will be published in peer reviewed high impact general medical and orthopaedic journals such as Lancet, the BMJ or similar.
- A summary of the study report, written in lay language will be produced and made available to participants, members of our user group and relevant patient-focused websites.

A full dissemination strategy will be produced for the trial.

14. Trial management

The Trial Co-ordinator role (split across two research fellows to allow full coverage during annual leave and other absences) will be based at YTU and will co-ordinate recruitment across the UK, supported by a senior Trial Manager.

14.1. Expertise of trial team

The multidisciplinary team includes expertise in surgical management of pilon fractures in both techniques being tested; experience of receiving treatment for a pilon fracture; physiotherapy; design, delivery and statistical analysis of randomised controlled trials; and design, delivery and analysis of qualitative research. The applicants are based at Hull and East Yorkshire (HEY) NHS Trust; The Royal Liverpool and Broadgreen University Hospitals NHS Trust; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences; Newcastle University and University of York.

Trial team name	Role	Institution
Mr Hemant Sharma	Chief Investigator	Hull and East Yorkshire NHS Trust
Dr Catriona McDaid	Surgical Trials Lead, York Trials Unit	University of York
Dr Stephen Brealey	Research Fellow	University of York
Professor David Torgerson	Director York Trials Unit	University of York
Mr Nikolaos Giotakis	Orthopaedic Consultant Surgeon	Royal Liverpool and Broadgreen University Hospitals Trust
Professor Matt Costa	Professor of Orthopaedic Trauma Surgery	University of Oxford and the John Radcliffe Hospital, Oxford
Ms Elizabeth Barron	Clinical Lead Physiotherapist	Hull and East Yorkshire NHS Trust
Mr Graham Gedney	Patient partner, Vice Chair of Patient Experience at Hull & East Yorkshire NHS trust	Hull and East Yorkshire NHS Trust
Prof Catherine Hewitt	Deputy Director, York Trials Unit	
Ms Ada Keding	Statistician	University of York
Mrs Belen Corbacho	Health Economist	University of York
Prof Joy Adamson	Prof of Applied Health Research & Ageing	University of Newcastle
Dr Arabella Scaltlebury	Research Fellow	University of York
Miss Lydia Flett	Trial Co-ordinator	University of York
Dr Deborah Sykes	Trial Co-ordinator	University of York
Dr Grace O'Carroll	Trial Co-ordinator	University of York
Mr Alex Mitchell	Trainee Statistician	University of York

15. Public Involvement

The PPI undertaken and planed as part of this grant follows both INVOLVE's guidance on undertaking PPI [56] and the 'Toolkit for meaningful and flexible involvement in trials' [57]. Prior to submitting the expression of interest, a meeting was held with two patients who had had a frame fixation. This informed the design of the trial and led us to add the qualitative study to the trial to ensure that we fully understand any barriers to maximum recruitment related to patient preferences.

A second local consultation was undertaken with a group of 14 people, including 10 patients who have had a pilon fracture, two of whom were public members of the patient experience group in Hull and East Yorkshire Trust and four relatives. We have supplemented this local

consultation by seeking input from five members of a newly formed National Trauma PPI Group, hosted by the University of Oxford. During these consultations the aspects covered were the relevance of the research question and planned outcomes, ethics, issues around patient preference, risks, burden, logistics, patient concerns, information and dissemination. Feedback from these consultations has been very positive, with PPI members stating that they thought this research is a priority for patients; that the outcomes are relevant for patients; that they could not see ethics issues or concerns with the risks or burdens for patients; and that the plain language summary was appropriate. However, during these consultations PPI members again highlighted that although patients would be very interested in the trial and willing to enrol, they might have strong preferences for certain surgical procedures, which could impact on recruitment. This supports the issues raised in our early discussion with patients which resulted in the plan to undertake the qualitative study, in order to explore and address recruitment barriers. Members highlighted that participants' restricted mobility needs to be taken into account when planning study assessments. Thus our planned follow-up method using postal questionnaires, where routine clinic visits were not planned, was felt to be appropriate. Clear explanations of the pros and cons of the interventions was also thought to be critical. Other suggestions from the group include sharing lay summaries of progress reports on a website, alongside details of lay involvement in the trial and flexible methods of follow-up. We plan to implement the suggestions above in the trial, with input from PPI members during the course of the trial.

A Patient Advisory Group (PAG) will meet during the set-up phase of the trial and help develop the detailed patient information to explain the risks and benefits of this study clearly. The PAG will review the consent process and advise on how to improve recruitment and retention, as well as the qualitative study exploring preference issues. The PAG will be invited to comment on the Case Record Form to ensure that all aspects of care considered important by patients are captured. The qualitative study will seek input from PPI members regarding the topic guide, participant recruitment and interpretation of results. The PAG will meet every 12 months, and will be chaired by Mr Gedney, our co-applicant, who has previously had an external frame fixation and is Vice Chair of Patient Experience at Hull & East Yorkshire NHS trust. Mr Gedney will be a member of the Trial Management Group and input into ongoing management of the trial where this relates to the patient experience. We will also approach a service user to be on the Trial Steering Committee and our costs cover this. This will allow the TMG/TSC to have reflections from patients when dealing with issues. The trial progress and findings will be discussed with the PAG. The ongoing collaboration will provide training. PPI members will be

invited to participate in disseminating findings, such as updating the entry on Wikipedia [54] and write the Map of Medicine entry on pilon fracture management [55]. In this way PPI members will actively participate in dissemination of the conclusions of this study in a manner that is accessible to patients.

16. Funding acknowledgement

This research is funded by the NIHR [name programme] (project number HTA - 15/130/84).

17. Department of Health disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

18. References

1. Marsh JL, S., *Axial-loading injuries: tibial plafond fractures*, in *Rockwood and Green's fractures in adults*, H.J. Bucholz RW, Court-Brown CM, Editor. 2006, Lippincott Williams & Wilkins Philadelphia.
2. Calori, G., et al., *Tibial pilon fractures: Which method of treatment?* Injury, 2010. **41**(11): p. 1183-1190.
3. Bedi, A., T.T. Le, and M.A. Karunakar, *Surgical treatment of nonarticular distal tibia fractures.* Journal of the American Academy of Orthopaedic Surgeons, 2006. **14**(7): p. 406-416.
4. Lee, Y.-S., et al., *Surgical treatment of distal tibia fractures: a comparison of medial and lateral plating.* Orthopedics, 2009. **32**(3): p. 163.
5. Topliss, C., M. Jackson, and R. Atkins, *Anatomy of pilon fractures of the distal tibia.* Journal of Bone & Joint Surgery, British Volume, 2005. **87**(5): p. 692-697.
6. Allen, D. *Tibial Plafond Fractures*. Ortho Bullets 2015 [cited 2015 22.10.2015]; Available from: http://www.orthobullets.com/trauma/1046/tibial-plafond-fractures.
7. Chowdhry, M. and K. Porter, *The pilon fracture.* Trauma, 2010. **12**(2): p. 89-103.
8. Jacob, N., et al., *Management of high-energy tibial pilon fractures.* Strategies Trauma Limb Reconstr, 2015: p. 1-11.
9. Hazarika, S., J. Chakravarthy, and J. Cooper, *Minimally invasive locking plate osteosynthesis for fractures of the distal tibia—results in 20 patients.* Injury, 2006. **37**(9): p. 877-887.
10. Sohn, O.J. and D.H. Kang, *Staged protocol in treatment of open distal tibia fracture: using lateral MIPO.* Clinics in orthopedic surgery, 2011. **3**(1): p. 69-76.
11. Bonar, S.K. and J. Marsh, *Tibial plafond fractures: changing principles of treatment.* Journal of the American Academy of Orthopaedic Surgeons, 1994. **2**(6): p. 297-305.
12. Pollak, A.N., et al., *Outcomes after treatment of high-energy tibial plafond fractures.* The Journal of Bone & Joint Surgery, 2003. **85**(10): p. 1893-1900.
13. Dischinger, P.C., et al. *Consequences and costs of lower extremity injuries*. in *Annual Proceedings/Association for the Advancement of Automotive Medicine*. 2004. Association for the Advancement of Automotive Medicine.
14. Sung, J.K., et al., *Reuse of external fixation components: a randomized trial.* Journal of orthopaedic trauma, 2008. **22**(2): p. 126-130.
15. NICE, *Fractures (complex): assessment and management of complex factures*, N.C.G. Centre, Editor. 2016, National Institute for Health and Care Excellence.
16. Mauffrey, C., et al., *Tibial pilon fractures: a review of incidence, diagnosis, treatment, and complications.* Acta orthopaedica Belgica, 2011. **77**(4): p. 432.
17. Willett, K.M., et al., *Orthopaedic trauma research priority-setting exercise and development of a research network.* Injury, 2010. **41**(7): p. 763-767.
18. Patil, S. and R. Montgomery, *Management of complex tibial and femoral nonunion using the Ilizarov technique, and its cost implications.* Journal of Bone and Joint Surgery-British Volume, 2006. **88B**(7): p. 928-932.
19. Kent, M., et al., *The service impact of failed locking plate fixation of distal tibial fractures: a service and financial evaluation at a major trauma centre.* European Journal of Orthopaedic Surgery & Traumatology, 2015: p. 1-10.
20. Murray, A.M., et al., *Cost description of inpatient treatment for ankle fracture.* Injury, 2011. **42**(11): p. 1226-1229.
21. Barron, E., et al., *Cost implications of the physiotherapy management of complex tibial fractures treated with circular frames.* Strategies in Trauma and Limb Reconstruction, 2013. **8**(3): p. 169-171.

22. MacKenzie, E.J., et al., *Health-Care Costs Associated with Amputation or Reconstruction of a Limb-Threatening Injury.* The Journal of Bone & Joint Surgery, 2007. **89**(8): p. 1685-1692.
23. Volgas, D., J.G. DeVries, and J.P. Stannard, *Short-term financial outcomes of pilon fractures.* The Journal of Foot and Ankle Surgery, 2010. **49**(1): p. 47-51.
24. Wang, C., et al., *Comparison of two-staged ORIF and limited internal fixation with external fixator for closed tibial plafond fractures.* Arch Orthop Trauma Surg, 2010. **130**(10): p. 1289-97.
25. Wyrsch, B., et al., *Operative treatment of fractures of the tibial plafond. A randomized, prospective study.* J Bone Joint Surg Am, 1996. **78**(11): p. 1646-57.
26. Richards, J.E., et al., *External fixation versus ORIF for distal intra-articular tibia fractures.* Orthopedics (Online), 2012. **35**(6): p. e862.
27. Costa, M.L., et al., *Percutaneous fixation with Kirschner wires versus volar locking plate fixation in adults with dorsally displaced fracture of distal radius: randomised controlled trial.* 2014.
28. Mittal, R., et al., *Factors affecting patient participation in orthopaedic trials comparing surgery to non-surgical interventions.* Contemporary Clinical Trials Communications, 2016. **3**: p. 153-157.
29. Abraham, N., et al., *Non-entry of eligible patients into the Australasian laparoscopic colon cancer study.* ANZ Journal of Surgery, 2006. **76**(9): p. 825-829.
30. Harrop, E., et al., *Why do patients decline surgical trials? Findings from a qualitative interview study embedded in the Cancer Research UK BOLERO trial (Bladder cancer: Open versus Lapararoscopic or RObotic cystectomy).* Trials, 2016. **17**(1): p. 1.
31. Potter, S., et al., *Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomised clinical trials in surgery? A qualitative study.* Trials, 2014. **15**(1): p. 1-10.
32. Salen, B.A. and R. Nordemar, *The Disability Rating Index: an instrument for the assessment of disability in clinical settings.* Journal of clinical epidemiology, 1994. **47**(12): p. 1423-1435.
33. Dawson, J., et al., *Responsiveness and minimally important change for the Manchester-Oxford foot questionnaire (MOXFQ) compared with AOFAS and SF-36 assessments following surgery for hallux valgus.* Osteoarthritis and Cartilage, 2007. **15**(8): p. 918-931.
34. Morley, D., et al., *The Manchester–Oxford Foot Questionnaire (MOXFQ): Development and validation of a summary index score.* Bone and Joint Research, 2013. **2**(4): p. 66-69.
35. Olerud, C. and H. Molander, *A scoring scale for symptom evaluation after ankle fracture.* Archives of Orthopaedic and Trauma Surgery, 1984. **103**(3): p. 190-194.
36. Oemar, M. and B. Janssen, *EQ-5D-5L User guide basic information on how to use the EQ-5D-5L instrument.* Rotterdam, The Netherlands: EuroQol Group, 2013. **28**.
37. Clint, S.A., et al., *The "Good, Bad and Ugly" pin site grading system: A reliable and memorable method for documenting and monitoring ring fixator pin sites.* Injury, 2010. **41**(2): p. 147-150.
38. Kellgren, J. and J. Lawrence, *Radiological assessment of osteo-arthrosis.* Annals of the rheumatic diseases, 1957. **16**(4): p. 494.
39. Achten, J., et al., *UK Fixation of Distal Tibia Fractures (UK FixDT): protocol for a randomised controlled trial of 'locking' plate fixation versus intramedullary nail fixation in the treatment of adult patients with a displaced fracture of the distal tibia.* BMJ Open, 2015. **5**(9).
40. Parsons, H., et al., *Measurement properties of the Disability Rating Index in patients undergoing hip replacement.* Rheumatology, 2014.

41. Ashby, R., et al., *A randomized trial of electronic reminders showed a reduction in the time to respond to postal questionnaires.* Journal of clinical epidemiology, 2011. **64**(2): p. 208-212.
42. Edwards, P., et al., *Increasing response rates to postal questionnaires: systematic review.* Bmj, 2002. **324**(7347): p. 1183.
43. Mitchell, N., et al., *Prior notification of trial participants by newsletter increased response rates: a randomized controlled trial.* Journal of clinical epidemiology, 2012. **65**(12): p. 1348-1352.
44. Mills, N., et al., *Training recruiters to randomized trials to facilitate recruitment and informed consent by exploring patients' treatment preferences.* Trials, 2014. **15**(1): p. 1.
45. Baker, S.E., R. Edwards, and M. Doidge, *How many qualitative interviews is enough?: Expert voices and early career reflections on sampling and cases in qualitative research.* 2012.
46. Council, M.R., *Good research practice: Principles and guidelines*, in *MRC ethics series*. 2012.
47. National Institute for Health and Care Excellence, *Guide to the methods of technology appraisal*. 2013, NICE.
48. Billingham, L., K.R. Abrams, and D.R. Jones, *Methods for the analysis of quality-of-life and survival data in health technology assessment.* Health Technology Assessment, 1999. **3**(10).
49. Manca, A. and S. Palmer, *Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials.* Applied health economics and health policy, 2005. **4**(2): p. 65-75.
50. Strauss, A. and J. Corbin, *Basics of qualitative research: Techniques and procedures for developing grounded theory*. 1998: Sage Publications, Inc.
51. Department of Health, *Research governance framework for health and social care*, D.o. Health, Editor. 2005.
52. Health Research Authority and UK Health Departments, *UK policy framework for health and social care research: issued for public consultation*, H.R. Authority, Editor. 2015.
53. MRC Ethics Series, *Good research practice: principles and guidelines*. 2012.
54. Wikipedia. *Wikipedia: pilon fracture*. 2016 [cited 2016 08/09]; Available from: https://en.wikipedia.org/wiki/Pilon_fracture.
55. Map of Medicine. *Map of Medicine*. 2016 [cited 2016 08/09]; Available from: http://mapofmedicine.com/.
56. INVOLVE, *Briefing notes for researchers: public involvement in NHS, public health and social care research*, N.I.f.H. Research, Editor. 2012.
57. Bagley, H.J., et al., *A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials – a work in progress.* Research Involvement and Engagement, 2016. **2**(1): p. 1-14.