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 is registered on International Standard Randomised Controlled Trial Number (ISRCTN98152560). The trial will also be registered with the Australian and New Zealand Clinical Trials Registry before recruitment commences in Australia.

Country Protocol Applies to: Australia

Protocol date and version number: Version 2.0 24 September 2021

United Kingdom Ethics Reference Number: 18/YH/0014

Australia Human Research Ethics Committee: Sydney Local Health District

Funder: The National Institute for Health Research Health Technology Assessment programme (reference number: 15/130/84). The trial budget in Australia will come from this funding.

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Synopsis

Scientific Title	External frame versus internal locking plate for articular pilon fracture fixation: a multi-centre randomised controlled trial	
Public title	Articular pilon fracture trial (ACTIVE)	
Countries of recruitment	United Kingdom and Australia and other countries	
Sponsor	UNSW will act as the sponsor for the trial for the sites within Australia. In its capacity as a sponsor within Australia, UNSW will be responsible for the conduct of the trial and will have the ability to vary the scope, suspend the clinical trial, or appoint or remove investigators.	
Health condition studied	Closed pilon fracture of the tibia, classified AO 43- C	
Interventions	**Arm 1:** Internal fixation: 'Locking' plate fixation with screws	**Arm 2:** External frame fixation: Limited open reduction and articular fixation using screws & fine wire fixator
Key Inclusion and Exclusion Criteria	INCLUSION CRITERIA: • Patients aged 18 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. • There are no absolute contraindications to either form of 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	
Trial Design	Parallel randomised controlled trial	
Trial Participants	Aged 18 years and older	
Planned Sample Size	334 or revised target of 250 (overall - from sites in Australia and other countries)	
Follow up duration	3, 6, 12 and 24 months	
Outcomes	Primary	Secondary

	Disability Rating Index (DRI) at 12 months	Olerud-Molander Ankle Score (OMAS); DRI; Health related quality of life (EQ5D-5L); Complications (including non-union); Resource use (e.g. impact on health care use and productivity).

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 in the UK 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. In addition the Orthopaedic Trauma Society in the UK 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 health care 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.

1. Aims and objectives

1.1. 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.

1.2. Objectives

Our objectives are to:

1. 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

2. 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 for the two treatment options

2. Trial design

An international, 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 both of which have been completed.

3. Methods

3.1. Setting

Patients will be recruited from hospitals in Australia and the United Kingdom (UK) and other countries that agree to take part.

3.2. Eligibility criteria

We will include all adult patients (18 years or older) with type C fractures who meet the eligibility criteria below.

3.2.1. Inclusion criteria

- Patients aged 18 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
- There are no absolute contraindications to either form of fixation

3.2.2. 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

3.3. 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.

3.3.1. 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.

3.3.2. 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.

3.3.3. 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 treating physiotherapists either through the public or private system, using a specific CRF.

3.4. Outcomes

3.4.1. 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.

3.4.2. Secondary outcomes

2. ***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 [33]. 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) [33]. 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.
3. ***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 [34]. 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.
4. ***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 [35]), rehospitalisation, blood clots, wound dehiscence, septic arthritis, secondary interventions for non-union and all other secondary procedures will be collected by the research team using CRFs for infections and medical records at 3, 6, 12 and 24 months.

4.1. 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 [36].

4.2. 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.

5. ***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.
6. ***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.
7. ***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.
8. ***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, 37, 38] 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.

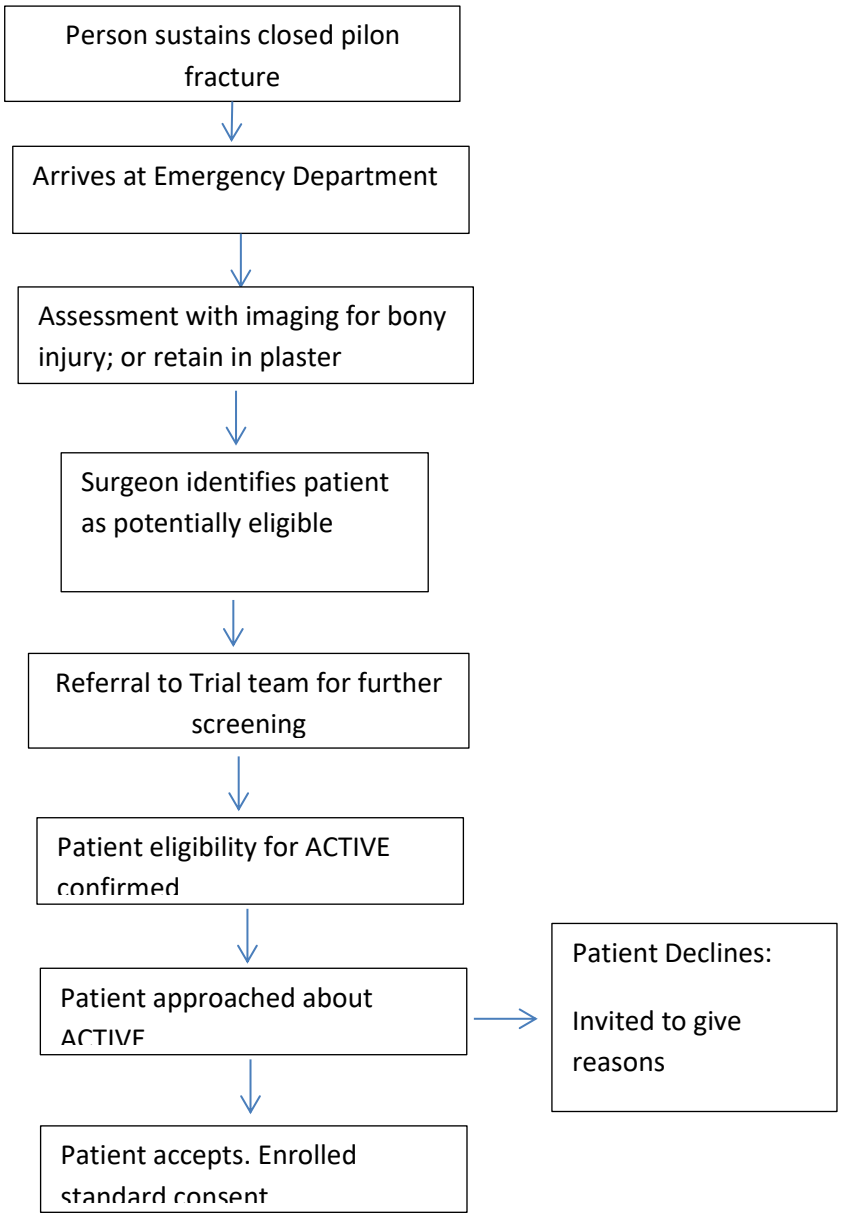
On 6th September 2021, the funder approved a request from the study team for a costed extension, with the proviso that the sample size be recalculated to provide 80% power. In order to detect a minimum clinically important difference of 8 points on the DRI (SD 20) with 80% power and 5% statistical significance, 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 a member of the research team 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. Participation of patients will be confirmed as written informed consent and voluntary to be consistent with the National Statement on Ethical Conduct in Human Research Section 2.2.9.

Figure 1: Pilon fracture treatment flowchart



4.6.2. Internal pilot

We have successfully completed a 12 month pilot study to test our assumptions about recruitment in the UK setting. The results of which informed the continuation of the trial and which will be published and publicly available in due course.

4.7. Randomisation

Randomisation will be undertaken by York Trials Unit (YTU). When patients have consented and their baseline forms have been completed, the recruiting research associate/nurse/clinician will send an electronic copy of the completed Eligibility Confirmation Form to YTU via the University of York's secure service for transferring files. A member of YTU staff will review the form and confirm patient eligibility to avoid inappropriate entry of patients into the trial. Once confirmed, YTU will randomise the patient using the secure web-based Trial Management System (developed specifically for the trial) and an email confirming treatment allocation will be sent to the research team at site. 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- 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 care.

4.8. Data collection methods

Data will be collected at recruiting sites from patients, then returned electronically 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.

YTU will not receive the names or contact details of any participants recruited at sites in Australia and will not have any direct contact with the Australian participants. The research teams at the Australian sites will securely store all consent forms and will not pass these on to YTU. The only personal identifiable data YTU will collect about participants recruited outside of the UK will be gender, date of birth, ethnicity, the hospital they were treated at and the country of residence. The Australian sites will do all the data collection described in the following sections in terms of patient questionnaires and hospital forms and will securely transfer these forms electronically to YTU.

4.8.1. Monitoring of Screening

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.

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. In addition, a 24-month follow up aligns with good practice timelines to assess for arthritis. All follow-up will be undertaken at routine clinic visits. Follow-up data of patient questionnaires may also be collected at 3, 6, 12 and 24 months at their routine follow up clinics. If a patient does not attend

their clinic appointment, the research team will send the questionnaire to the patient via mail or email, and may follow this up with a reminder phone call. 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. Research staff at the Australian sites will ask patients for full contact details (including mobile phone number and email address) but will not share these details with YTU. Patients will primarily attend hospital clinics to complete questionnaires but when feasible, or necessary, 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. We will also send 2 and 4 week reminders. Where these methods fail we will give participants the option to complete 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.

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.

5. Data management

Data will be stored, accessed and archived according to the Australian Privacy Principles set out in the Australian Privacy Act 1988 as well as relevant state and territory privacy laws. The trial team will also adhere to the European Union General Data Protection Regulation as enshrined in the UK's Data Protection Act 2018 for the data stored in YTU. 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 prior to sending to YTU and 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. This includes in all correspondence with YTU about the patient,

The following data will not be sent to YTU: participant status log, participant enrolment log and consent forms. Instead of sending YTU copies of the consent forms, sites will complete a checklist to confirm the correct completion of consent forms. YTU will perform remote annual compliance checks with participating hospitals as this is a low risk study comparing treatments that are standard medical care. There will also be central monitoring by the independent oversight committees in the UK i.e. Trial Steering Committee and Data Monitoring Ethics Committee. UNSW as the Sponsor in Australia will have primary responsibility for the conduct of the trial at the sites in Australia but overall conduct of the trial across all countries will be reviewed on their behalf by the UK Trial Steering Committee and Data Monitoring Ethics Committee. UNSW will also have the ability to vary the scope, suspend the clinical trial, or appoint or remove investigators.

The sites will be provided with a spreadsheet to allow them to track when hospital forms and patient questionnaires are due. The spreadsheet will be automated so that when the randomisation date is entered the due dates for data to be collected are populated.

5.1. Data entry

The data collected by sites using paper CRFs, will be scanned and then sent electronically to YTU using a secure service and will be entered/scanned into a secure web-based interface, specifically developed for this study.

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.

5.2. Data storage

Each site will hold data according to the Australian Privacy Principles set out in the Australian Privacy Act 1988 as well as relevant state and territory privacy laws. The trial team will also adhere to the European Union General Data Protection Regulation as enshrined in the UK's Data Protection Act 2018 for the data stored in YTU. 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. YTU are undertaking the analyses of the data collected and will only keep data that are anonymised. This anonymised data are stored on servers which are anti-virus protected and physically stored in a building that has 24 hours security with full data backups performed daily. 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 fifteen 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).

Anonymised data collected during the study may be stored indefinitely. This anonymised data may be used for other analyses in the future. The anonymised data may also be shared or pooled with other collaborators both in Australia and other countries. Any identifying information will be kept strictly confidential, and access will be limited to the original study team at participating hospital in Australia. Researchers who analyse the anonymised data in the future will be unable to identify trial participants.

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 at the participating hospitals. 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 [39]. All paper records will be stored in a secure storage facility YTU or in the longer term transferred to a secure off-site storage facility. All electronic records will be stored on a password protected server.

5.3. Quality Assurance and Quality Control

In the UK this study will be fully compliant with the Research Governance Framework and MRC Good Clinical Practice Guidance. In Australia we will comply with the National Statement on Ethical Conduct on Human Research, Declaration of Helsinki and Good Clinical Practice (with reference to The Australian Clinical Trial Handbook and the Australian Code for the Responsible Conduct of Research).

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 YTU working closely with hospital staff at the participating sites in Australia and meeting the requirements of the UNSW Sponsor for sites in Australia. 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 YTU to ensure integrity of randomisation, study entry procedures and data collection.

A delegation log defines the trial responsibilities of the UNSW Sponsor's Delegate, the Coordinating Principal Investigator, site Principal Investigators and the trial-related personnel. The delegation log specifies the responsibilities for the conduct, oversight and monitoring for the trial that are delegated to the Coordinating Principal Investigator. The delegation log includes the trial-related responsibilities that may be delegated to the approved Principal Investigators and/or trial related personnel who are qualified by training or experience to do this. The delegation log specifies what the UNSW Sponsor's Delegate should be notified of.

The study will be conducted at participating sites at which expression of interest forms have been completed, feasibility assessed and training delivered. The Coordinating Principal Investigator will ensure the appropriate selection and feasibility of sites according to the requirements of the Sponsor. There will be a suitably qualified and experienced Principal Investigator at each site and site personnel will provide copies of CVs, Good Clinical Practice training certificates and records of relevant qualifications. The participating site will also have approvals in place for authorising the commencement of the trial. Regular monitoring will be conducted at the sites to assess progress with screening; correct completion of consent forms; assessment of CRFs for completion, accuracy, and whether any duty of care issues need following-up on; as well as annual remote monitoring by YTU with the sites to confirm the trial is following all the correct procedures and the above is being implemented. When necessary findings will be escalated to the Principal Investigator at the site, R&D delegate at the site, and Sponsor for corrective action.

5.3.1 Protocol deviations and serious breaches

A protocol deviation is defined as any breach, divergence or departure from the requirements of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval and does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the research or clinical trial. Protocol deviations are events that do not occur in a persistent or systematic manner, and do not have the potential to result in participant harms.

Protocol deviations occurring at a site must be documented in site files and need to be reported by site principal investigator to the Coordinating Principal Investigator. The Coordinating Principal Investigator must review the protocol deviation, along with the clinical trial protocol to establish the corrective actions and preventative steps to prevent the deviation from reoccurring. The protocol deviation and corrective action plan must be reported to the UNSW Sponsor's Delegate by the Coordinating Principal Investigator or Coordinating Research Team using the protocol deviation report form.

A serious breach is defined as a breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. A serious breach occurring at a participating site must be reported by the site Principal Investigator to the Coordinating Principal Investigator within a specified timeframe. The Coordinating Principal Investigator must review the serious breach, along with the clinical trial protocol to develop a Corrective and Preventive Action (CAPA) that defines the steps to prevent the serious breach from reoccurring. The serious breach report and the CAPA is to be provided to the approving HREC and the UNSW sponsors delegate for review and approval. A Suspected Breach form must also be completed when a third party (e.g. individual / institution) wishes to report a suspected breach of Good Clinical Practice or the protocol. This should be reported directly to the reviewing HREC without reporting through the sponsor.

A register of protocol deviation and serious breach reports must be recorded, written records and copies of documentation sent to the UNSW sponsor and must be retained in the Investigator Site File. Copies of protocol deviation and serious breach reports must be recorded, written records and copies of documentation sent to the UNSW sponsor, referrals

made to the HREC or to establish whether a breach of the Australian Code for Responsible conduct of research must be retained in the Trial Master File in the UK.

The UNSW Sponsor's Delegate will review reports to establish whether the event meets the definition of a protocol deviation or serious breach, to establish whether the proposed CAPA is appropriate and to establish whether there is or will be an ongoing impact on the reliability and robustness of the data generated.

Feedback from the approving HREC will be sought regarding the UNSW Sponsor Delegate's proposed corrective and preventive actions.

Protocol deviation and/or serious breach reports where a UNSW researcher, staff or student is responsible for the protocol deviation or the serious breach will be reviewed as per the UNSW Research Misconduct Procedure to establish whether a breach of the UNSW Research Code of Conduct has occurred.

Protocol deviation and/or serious breach reports where the UNSW Sponsor's Delegate determines that the site Principal Investigator(s)/ site personnel are responsible for a protocol deviation or the serious breach will be referred onto their responsible institution for review under their own Research Misconduct procedures to establish whether a breach of the Australian Research Code for the Responsible Conduct of Research has occurred.

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). YTU will be responsible for the statistical analyses of all trial data.

5.4.3. Statistical analysis

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 included in the primary analysis i.e. those who

provided a DRI score at 3 months, 6 months or 12 months, and had data on fracture type. 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 data will be summarised as means, standard deviations, medians and ranges; categorical data will be summarised as frequencies and percentages.

The primary analysis model will be a covariance mixed effects linear regression model, with DRI scores at 3, 6 and 12 months follow-up as the dependent variable, adjusting for randomised treatment arm, group by time interaction and fracture type (C1 or C2 vs C3) as fixed effects and including treating centre and patient as random effects. 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). A sensitivity analysis will be carried out to assess the impact of adjusting for the DRI pre-injury and post-injury. Missing values of the DRI at baseline will be imputed using centre-specific means. The primary analysis model will then be repeated with the addition of terms adjusting for the DRI pre-injury and post-injury. A sensitivity analysis will be carried out to explore the impact of international sites on the primary outcome analysis results.

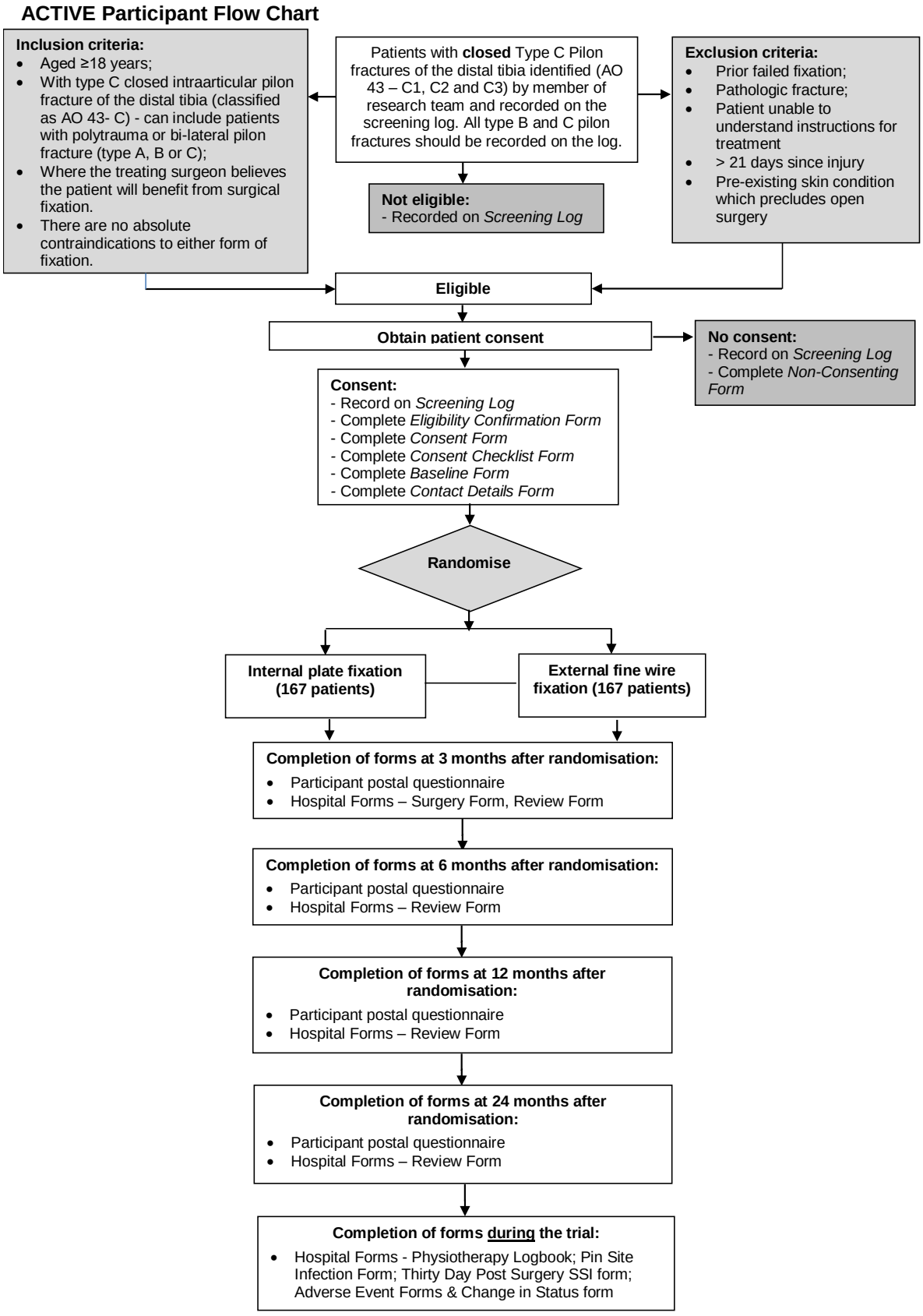
The nature of missingness for outcome data will be explored and multiple imputation and/or deviations from the missing-at-random assumption considered if appropriate.

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. The p-values of the interactions 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 (<2 days versus 2-7 days versus >7 days).

Secondary continuous PROMS outcomes will be analysed in a similar manner to the primary analysis model. Binary secondary outcomes of additional procedures and complications will be analysed graphically.

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 time horizon of the analysis will be 2 years, as per duration of the ACTIVE trial, and will follow a National Health Services (NHS) and Personal Social Services (PSS) UK perspective. In addition, we will conduct a secondary analysis to explore the impact of productivity costs and unpaid activities on cost-effectiveness results. Any pre-specified sub-group analyses will be conducted based on the subgroups defined by the statistical analysis.

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. Costs relating to surgical procedures will be based on time in theatre, staff time, consumables and devices, and nights in hospital after the procedure. 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 [40].

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 [41].

For the analysis, regression methods will be used following a bootstrap framework. The bootstrap's main advantage is dealing with skewed data, which often characterise economics data. Heterogeneity will be captured by including baseline prognostic factors in regressions that will inform the economic model. Selection of regression covariates will be in line with the statistical analyses. The pattern of missing data will be analysed and handled by means of multiple imputation (MI)[42]. A range of sensitivity analysis will be conducted to test the robustness of the results under different scenarios, including probabilistic sensitivity analysis. The probability that each intervention is cost-effective will be reported at the cost-effectiveness thresholds applied by NICE of £20,0000 to £30,000/QALY [43] and also £13,000/QALY as suggested by recent research [44, 45]. If the results deem appropriate (i.e. there is a non-dominant situation in the trial based evaluation) a complementary analysis will be carried out 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 trial to a life time horizon. A review of existing literature will be conducted to

determine the existence of evidence of relevant treatments in the patient groups eligible for the ACTIVE trial that could be potentially used in our model.

To note that this cost-effectiveness assessment will be conducted from the UK NHS perspective. Therefore, only economic data collected from participants recruited from UK sites will be used for the primary analysis. However, country specific cost-effectiveness estimates will be explored via sensitivity analyses if local unit costs from these jurisdictions are facilitated.

Full analyses will be detailed in a Health Economic Analysis Plan (HEAP) and will be the responsibility of YTU.

5.5. Data monitoring

The primary responsibility for monitoring the safety of participants enrolled in the clinical trial in Australia lies with the UNSW Sponsor. Data monitoring will be undertaken by the Trial Management Group (TMG), Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) that are already set up in the United Kingdom on behalf of the UNSW Sponsor. This is so that there is oversight of safety data for all trial participants. All safety reporting for data collected for participants enrolled at sites in Australia will still be reported to the UNSW Sponsor as described in the later section about adverse event management.

5.5.1. Trial Management Group (TMG)

A TMG has been established to oversee the day-to-day management of ACTIVE in the UK, and is chaired by the Chief Investigator in the UK. 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 regularly by tele/videoconference and will also meet regularly with international collaborators.

In Australia, Associate Professor Sam Adie is the Co-ordinating Principal Investigator for the multiple sites involved in undertaking the ACTIVE trial and is the UNSW staff member who is initiating the clinical trial. Meetings will also be held quarterly (or more regularly if required) between the Principal Investigators in Australia which Associate Professor Sam Adie will chair. Other trial personnel will be invited from hospital sites in Australia and also YTU to facilitate preparing of progress reports, discussion at the meeting and the recording of minutes. The

UNSW Sponsor Delegate will be invited to attend these meetings and will receive copies of the minutes which will be kept in the Investigator Site Files and the Trial Master File in the UK.

5.5.2. Trial Steering committee (TSC)

An independent TSC in the UK has been established to provide overall supervision for ACTIVE 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 in the UK 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 in the UK 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 adverse events. 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.

5.5.4 Role of UNSW Sponsor

UNSW as the Sponsor in Australia will have primary responsibility for the conduct of the trial at the sites in Australia. The overall conduct of the trial across all countries will be reviewed on their behalf by the UK Trial Steering Committee and Data Monitoring Ethics Committee. UNSW will be updated with the reports of these committees and the minutes of these meetings.

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 for the UK sites [46, 47] [48] and in Australia will also comply with the National Statement on Ethical Conduct on Human Research, Declaration of Helsinki and Good Clinical Practice (with reference to The Australian Clinical Trial Handbook and the Australian Code for the Responsible Conduct of Research). It is not expected that this trial will disproportionately affect the indigenous population. The participant information sheet for the study has been developed with the involvement of service users and gives a balanced account of the possible benefits and known risks of the interventions. It states 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. We will not recruit patients who do not have the capacity to understand the instructions for treatment. An application for 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 as explained in the preceding section.

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

Informed consent will be obtained by trained members of the research team using a patient information leaflet developed with the help of service users, which explains the risks and benefits clearly. Participation of patients will be confirmed as written informed consent and

voluntary to be consistent with the National Statement on Ethical Conduct in Human Research Section 2.2.9. 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 occurrence (medical or other) in a clinical trial participant administered one or more of the trial interventions. These AEs will be assessed for their 'expectedness' and 'relatedness' with the intervention(s) by the site investigator. A list of expected adverse events is given in Table 2. We will only collect adverse event data that are unexpected and related to treatment for the original injury and only up until the 24 month follow up. All AEs will be listed on the appropriate Case Report Form for routine return to YTU. Non-serious AEs will need to be reported to YTU within five days from when they are known at the site.

Serious adverse events are defined as any event 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.

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 sent to YTU using the agreed secure electronic service within 24 hours of the local

investigator becoming aware of them. The causality and expectedness will be assessed by the local site investigator in Australia.

A person of experience and training (Mr Ashish Diwan), who is independent of the listed investigators, will assess the causality and expectedness of all adverse events and ensure the appropriate action is taken. All adverse events will be reported to the Trial Management Group, Trial Steering Committee and Data Monitoring Committee in the UK at their next meetings as explained in Section 5.3.

Follow up reports a month later will be reviewed by Mr Ashish Diwan to ensure that adequate action has been taken and progress made for providing support and care to participants.

A safety monitoring register of reported events and an assessment of trial safety will be reported to the UNSW Sponsor's Delegate annually.

A significant safety issue is defined as any issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. An urgent safety measure is defined as a measure required to be taken to eliminate an immediate hazard to a participant's health or safety. Any significant or urgent safety issues will be reported to the UNSW Sponsor's delegate immediately but no later than seven days.

7. Research ethics approval

We will seek approval from a Human Research Ethics Committee certified by the National Health and Medical Research Council to review multi-centre research. Once approval is gained, site specific governance approval will be sought from each participating centre. We do not anticipate major ethical concerns with this study. We will submit to the multi-centre HREC at Sydney Local Health District whose mailing address is Research Ethics and Governance Office (REGO), Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW, 2050.

7.1. Protocol amendments

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

7.2. Consent

A member of the research team 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. Participation of patients will be confirmed as written informed consent and voluntary to be consistent with the National Statement on Ethical Conduct in Human Research Section 2.2.9.

7.2.3. Documenting consent

The original signed consent form will be kept in the investigator site file. Two additional copies of the consent forms will be made; one to be held in the patient's medical notes and one for the patient. Site staff will not return any consent forms to YTU but will instead complete a checklist to confirm that the consent form has been completed correctly and this will be returned to YTU electronically using the agreed secure service in place of the consent form to maintain patient anonymity.

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

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 and in all correspondence with YTU; patients will not be identified by their name in order to 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 UNSW Sponsor, the participating hospital, 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. Compliance with the therapeutic goods act

The surgical techniques under investigation are well-recognized and international accepted surgical procedures using approved implants and medical devices that are routinely used for the

indication outlined in this trial within their marketing authorisation. We do not therefore require prior authorisation by the Therapeutic Goods Administration.

8. Plan of investigation and timetable

The start date for the study was 1 September 2017 with a 60 month duration. With a 32 month extension to the project the study will now be 92 months in duration and end 30th April 2025. Recruitment began on 1 March 2018 and will end on 31 October 2023.. Data collection will end on 31 October 2024 and analyses and write up completed on 30th April 2025..

9. 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 in the UK, international collaborators and study Sponsors for their respective countries.

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

10. Indemnity

The treatment options for this fracture population are both routine and currently available; therefore, the risk of patients coming to harm is minimal.

In Australia, individual surgeon medical indemnity covers them for involvement in clinical trials as stipulated in the Report to the National Health and Medical Research Council. Insurance will also be provided by the Trial Sponsor in Australia. UNSW insurance and the legal agreements will be negotiated once the UNSWs role as the Sponsor has been confirmed.

11. Finance

The Funder in the UK is the NIHR Health Technology Assessment programme. There is a collaboration agreement between the UK Sponsor and University of York which agrees on responsibilities and finances on behalf of the Funder. There is a budget of £599.88 per participant to cover the cost of collection of baseline data and participant follow-up. These costs are being funded by the NIHR in the UK with whom the UK Sponsor holds the budget that will be contracted to University of York to be provided to the Sponsor in other countries. The UNSW Sponsor will administer the funding for the trial to sites via the UNSW research grants and contracts team.

12. 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 in the UK and society and more broadly to Australia and other countries if there are sufficient numbers. 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 [49] and write the Map of Medicine [50] entry on pilon fractures management.
- The results of the study will be presented at national and international surgical meetings such as the Australian Orthopaedic Association Annual Scientific Meeting, The Australian Orthopaedic Trauma Society Meeting, the Australian Orthopaedic Foot and Ankle Society Meeting, 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 publication policy will be produced for the trial. This will ensure that all Principal Investigators at sites will be listed as named Collaborators on the Final Report and main publication.

13. Trial management

The Trial Co-ordinator role will be based at YTU and will co-ordinate recruitment across the UK and international sites, supported by a senior Trial Manager. The UNSW Sponsor of the trial will enter into a clinical trial research agreement with each site that will outline the payments to sites for data collection. Recruitment and data collection will not commence at a site until the agreement is in place and there is authorisation from the site to commence the study. The YTU team will work closely with the Coordinating Principal Investigator, the Principal Investigators at the other sites and the UNSW Sponsor. The UNSW Sponsor via the

Coordinating Principal Investigator and the YTU team will be responsible for all the activities to be undertaken to ensure the criteria are met for UNSW to be the Sponsor of an investigator-initiated trial (see https://research.unsw.edu.au/clinical-trials-research-governance). This includes being responsible for conducting the trial according to this protocol that is consistent with the UK protocol and other countries. The UNSW Sponsor's Delegate will provide written confirmation of the UNSW sponsor-related responsibilities for the trial before recruitment and data collection can commence.

13.1. Expertise of trial team

The multidisciplinary team in the UK 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 UK team are based at Hull University Teaching Hospitals NHS Trust; The Royal Liverpool and Broadgreen University Hospitals NHS Trust; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences; and University of York. The trial team also comprises of the Principal Investigators (Professors/Consultant Orthopaedic Surgeons) at the participating sites in Australia, including Associate Professor Sam Adie as the Coordinating Principal Investigator.

14. Public Involvement

The PPI undertaken and planned as part of this grant follows both INVOLVE's guidance on undertaking PPI [51] and the 'Toolkit for meaningful and flexible involvement in trials' [52]. Prior to submitting for funding, 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 was 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) met 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 reviewed the consent process and advised on how to improve recruitment and retention, as well as the qualitative study exploring preference issues. The PAG commented on the Case Record Form to ensure that all aspects of care considered important by patients are captured. The qualitative study sought input from PPI members regarding the topic guide, participant recruitment and interpretation of results. The PAG will meet every 12 months. Mr Gedney, our co-applicant, who has previously had an external frame fixation, will be a member of the Trial Management Group and input into ongoing management of the trial where this relates to the patient experience. A service user is on the Trial Steering Committee. 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 [49] and write the Map of Medicine entry on pilon fracture management [50]. In this way PPI members will actively participate in dissemination of the conclusions of this study in a manner that is accessible to patients.

15. References

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