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A multicentre, randomized, parallel group, superiority study to compare the clinical effectiveness and cost-effectiveness of external frame versus internal locking plate for complete articular pilon fracture fixation in adults

PROTOCOL FOR THE ACTIVE RANDOMIZED CONTROLLED TRIAL

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Aims

A pilon fracture is a severe ankle joint injury caused by high-energy trauma, typically affecting men of working age. Although relatively uncommon (5% to 7% of all tibial fractures), this injury causes among the worst functional and health outcomes of any skeletal injury, with a high risk of serious complications and long-term disability, and with devastating consequences on patients' quality of life and financial prospects. Robust evidence to guide treatment is currently lacking. This study aims to evaluate the clinical and cost-effectiveness of two surgical interventions that are most commonly used to treat pilon fractures.

Methods

A randomized controlled trial (RCT) of 334 adult patients diagnosed with a closed type C pilon fracture will be conducted. Internal locking plate fixation will be compared with external frame fixation. The primary outcome and endpoint will be the Disability Rating Index (a patient self-reported assessment of physical disability) at 12 months. This will also be measured at baseline, three, six, and 24 months after randomization. Secondary outcomes include the Olerud and Molander Ankle Score (OMAS), the five-level EuroQol five-dimenison score (EQ-5D-5L), complications (including bone healing), resource use, work impact, and patient treatment preference. The acceptability of the treatments and study design to patients and health care professionals will be explored through qualitative methods.

Discussion

The two treatments being compared are the most commonly used for this injury, however there is uncertainty over which is most clinically and cost-effective. The Articular Pilon Fracture (ACTIVE) Trial is a sufficiently powered and rigorously designed study to inform clinical decisions for the treatment of adults with this injury.

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Introduction

A pilon fracture is a severe fracture of the distal end of the tibia, involving its weight-bearing articular surface at the ankle joint. 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 a traffic accident.[1,2] Although pilon fractures are relatively uncommon—5% to 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

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Table I. Trial objectives.

1	To determine the effectiveness of external fixation versus internal fixation for the treatment of Type C pilon fractures. This will be achieved through undertaking a parallel group multicentre RCT, using the primary outcome measure, the DRI which is a patient-reported outcome measure assessing patient function at 3, 6, 12, and 24 months. The primary timepoint is assessment of DRI at 12 months after randomization.
2	Undertake a 12-month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility.
3	To explore barriers and facilitators during the pilot phase in order to optimize trial procedures and recruitment rates.
4	Undertake an economic evaluation to compare the cost-effectiveness of the two treatment options to determine the most efficient provision of future care and to describe the resource impact on the NHS for both treatments.

DRI, Disabilty Rating Index; RCT, randomized controlled trial.

extensive soft-tissue damage that challenge repair.[7] This is particularly the case for complete articular fractures (Type C). Complications are common here, including deep infection, osteomyelitis, repeat unplanned surgery including arthrodesis, and amputation with the resultant impact on quality of life.[8] Complications can result in readmission rates of up to 50%.[7,9,10] Post-traumatic 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. Internal fixation uses a plate and screws to stabilize the fracture. One-third of patients with external wires and pins develop infection.[15] Although fine wire fixation is associated with a high superficial infection rate, it may lead to less deep infection, amputation, and lower secondary intervention rate compared with plates.[16]

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 randomized controlled trials (RCTs), to assess whether internal or external fixation is better for definitive management of these injuries.[2,16,17]

In order to address the evidence gap we will undertake a RCT and economic evaluation to establish whether internal or external fixation is more clinical effectiveness and cost-effective for the management of Type C pilon fractures. The injury's rarity means that the involvement of the maximum numbers of centres possible that 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 optimized before proceeding to the full trial.

Objectives

The aim of this study is to provide good quality evidence of 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. The specific objectives are listed in Table I.

Methods

Trial design. ACTIVE is a pragmatic, multicentre, randomized controlled superiority trial with parallel groups, allocated on a 1:1 ratio. A concomitant economic evaluation and a nested qualitative study with trial participants and healthcare professionals will be included. An internal 12-month pilot study will confirm feasibility and inform trial processes.

Study setting. Patients will be recruited from NHS hospitals across the UK, with recruitment from a minimum of 23 sites required. Inclusion of international sites will also be explored.

Eligibility criteria. Included patients must meet all of the eligibility criteria, which are presented in Table II. Patient eligibility for the study will be confirmed by a local consultant orthopaedic surgeon or delegated clinician prior to their recruitment and recorded on the Case Report Form (CRF).

There will be no specific requirements in place on who can deliver the surgical procedures or routine physiotherapy. This will be as per routine clinical practice at the participating centre. It will be confirmed during set-up that both interventions can be delivered at participating sites. The level of experience of surgeons and physiotherapists treating trial participants will be recorded, in terms of their grade and the average number of pilon fracture patients they treat.

Interventions

Surgeons at recruiting centres will perform the surgery according to the patients' random allocation.

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 at 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.

Table II. Patient eligibility criteria

Inclusion criteria
Aged ≥ 16 years
Closed intra-articular pilon fracture of the distal tibia classified according to AO: AO 43-C1, C2 and C3 (complete articular), including patients with a bi-lateral pilon fracture and who have polytrauma.
The treating surgeon believes the patient will benefit from surgical fixation.
Exclusion criteria
> 21 days since injury
Previous failed fixation
Pathological fracture
Pre-existing (pre-injury) skin condition which precludes open surgery
Patient is/would be unable to understand instructions for treatment

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, and number of rings, wires, and half pins will depend on the fracture configuration and will be 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.

Physiotherapy. All participants will receive standardized, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. In this pragmatic trial, any other rehabilitation input including and beyond written physiotherapy advice will be left to the discretion of the clinical team. Data on rehabilitation will be collected using patient-completed questionnaires at three, six, 12, and 24 months post-randomization, as well as in a specific hospital CRF.

Primary outcomes. The primary outcome measure is the Disability Rating Index (DRI) at 12 months post-randomization. The DRI is a validated patient-reported outcome measure questionnaire.[18] It consists of a 12-item visual analogue scale questionnaire assessing the patients' own rating of their disability specifically related to the lower limb (DRI; score range, 0 (no disability) to 100 (complete disability)). These data will be collected at baseline, three, six, 12, and 24 months follow-up post-randomization. Baseline assessment will ask participants about their functioning before their injury and before their surgery.

Secondary outcomes. These will be assessed at baseline, 3, 6, 12, and 24 months post-randomization unless otherwise stated: The Olerud and Molander Ankle Score (OMAS) is an established nine-item, patient-reported outcome measure developed and validated for use in clinical trials assessing symptoms following ankle fracture.[19] It contains items assessing pain and various activities of daily living. Item responses are each scored from 0 to 25, with 0 representing the most severe state. Raw scale scores are then converted to a metric (0 to 100; 0 = most severe).[19] At baseline, the OMAS will be collected once (patients will be asked to complete it thinking about the week before ankle fracture).

The five-level EuroQol five-dimension questionnaire (EQ-5D-5L) is a validated measure of health-related quality of life assessed in terms of 5 dimensions and a separate visual analogue scale. The EQ-5D-5L will be scored according to the User Guide (EQ-5D-5L; utility score range from < 0 (where 0 is a health state equivalent to death; negative values are equivalent to states worse than death) to 1 (full health)).[20] EQ-5D-5L data will be collected twice at baseline: to assess patient health related quality of life on the day (after the injury), and for the week before injury. At baseline, the EQ-5D-5L will be collected before randomization by patients who have capacity to consent at that time; or at the earliest opportunity after randomization, by patients who consent having regained capacity.

Data on all further surgical procedures and other complications will be collected. This includes deep wound infection (using Centres for Disease Control and Prevention definition,[21] superficial infection, pin site infection (defined using the 'Good, Bad and Ugly' pin site grading system),[22] rehospitalization, blood clots, wound dehiscence, septic arthritis, and secondary interventions for nonunion). Also recorded will be an assessment of nonunion (defined as inability to heal as confirmed on radiographs/CT scan or as a secondary intervention for failure to heal); malunion (defined by as standard measurement based on Dror Paley's technique,[23] assessed from final radiographs at 12 months); and secondary arthritis in the ankle (assessed using the Kellgren and Lawrence scale).[24] Routine imaging at 12 months after the injury will be used for these assessments (anteroposterior and lateral tibia radiograph views, with a focus on the ankle) and/or when clinically indicated a CT scan of the tibia, fibula, and/or ankle.

Data concerning resource use and work impact will be collected to inform the economic evaluation from patient questionnaires and hospital records (e.g. length of hospital stay, rehospitalization, and return to work). Patients will be asked about their treatment preferences at baseline and at 12 months follow-up.

Participant timeline. Participants will be followed up at three, six, and 12 months post-randomization, with the primary endpoint being 12 months post-randomization. There will be an additional secondary outcome endpoint of 24-month follow-up for all patients recruited in the first 24 months of the trial (approximately two-thirds of the total sample) to help reduce costs and length of the trial.

Figure 1 illustrates the overall schedule and flow of trial participants through the study, based on the recommended figure in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[25] from initial

TIMEPOINT	Pre-randomisation	Randomisation	Treatment delivery	30 days post-surgery	3 months post-randomisation	6 months post-randomisation	12 months post-randomisation (primary end point)	24 months post-randomisation
ENROLMENT:								
Eligibility screen/ confirmation of eligibility	X							
Informed consent	X							
Baseline questionnaire *(patient demographics, PROMs[a], patient medical background[b], patient preference for treatment)*	X							
Treatment allocation		X						
INTERVENTION:								
Internal plate fixation			X					
External frame fixation			X					
Physiotherapy[c]		◆	—	—	—	—	◆	
ASSESSMENTS:								
Patient questionnaire *(including the primary outcome; DRI, EQ-5D-5L, OMAS, resource use, rehabilitation details)*	X				X	X	X	X
Physiotherapy data[d]		◆	—	—	—	—	◆	
Operation data *(e.g. surgeon experience, duration of surgery, details of fixation)*			X					
Assessment for deep infection				X	X	X	X	X
Assessment for superficial infection				X	X			
Assessment for pin site infection[e]			◆	—	—	◆		
Complications relating to injury/treatments *(e.g. delayed wound healing, wound dehiscence)*					X	X	X	X
Medical and surgical complications *(e.g. Deep Vein Thrombosis)*					X	X	X	X
Secondary procedures *(e.g. amputation, wound debridement, removal/adjustment of metalwork)*					X	X	X	X
Bone healing assessment[f]							X	
Adverse events		◆	—	—	—	—	—	◆

Fig. 1

Overall schedule of events for the Articular Pilon Fracture (ACTIVE) trial, from eligibility screening, enrolment, treatment and follow-up assessments. [a]Patient-reported outcome measures collected at baseline include the Disability Rating Index (DRI), Olerud and Molander Ankle Score (OMAS), and five-level EuroQol five-dimension score (EQ-5D-5L). [b]Patient medical background includes details on whether the patient is diabetic or is immunosuppressed, and details of any polytrauma present at baseline. [c]All trial patients will receive standardized written physiotherapy advice. Any further rehabilitation input throughout their treatment pathway will be at the discretion of the clinical team. [d]Physiotherapy logbooks completed to record all rehabilitation delivery within the Trust starting from enrolment. [e]Assessment for pin site infections will be made each time a patient with an external frame attends a hospital visit until the time that the frame is removed, generally before six months, and recorded on a specific Case Report Form (CRF). [f]Routine imaging will be used to complete the bone healing assessment at 12 months post-randomization to assess for malunion, nonunion, and secondary arthritis.

eligibility screening, consent and randomization, treatment delivery, and data collection timepoints.

Sample size. In order to detect a minimum clinically important difference of eight points on the DRI (SD 20)[18,26,27] with 90% power and 5% statistical significance, 133 participants per group are required (calculated using nQuery software (Statsols, Ireland)). Accounting for 20% attrition at the primary endpoint of one-year follow-up, the total recruitment target is 334 participants (167 per arm).

Recruitment. Potentially eligible patients will be identified from orthopaedic trauma clinics or wards, intensive care units, and the emergency departments at participating centres. All patients with a suspected type C pilon fracture will be screened for eligibility by the research team at the centre. Figure 2 outlines the pilon fracture treatment flowchart and how it fits into our recruitment plans for the trial.

Once patient eligibility is confirmed, a member of the patient's direct care team will approach them about the study. The research nurse/associate will provide information about the study including the participant information sheet and information leaflet about pilon fractures. Patients will have the opportunity to ask questions of the surgeon and the local research team. A document will be available to sites that answers frequently asked questions patients may have about the treatment options. Consent will be sought for follow-up beyond the duration of the trial to allow the possibility of future long-term follow-up.

Due to the nature of the injury and its treatment, some patients may be unconscious at the time of admission, all will be distracted by their injury and its implications, and may have been administered large doses of opiates for pain relief. In instances where informed consent cannot be obtained from the patient a personal or professional consultee will be consulted in line with the Mental Capacity Act 2005 for patients recruited within England and Wales. Differences in research legislation and legal frameworks around recruitment of adults with incapacity in Scotland and Northern Ireland means that recruitment via consultee will not be used in these countries. In instances where a personal or professional consultee has agreed on behalf of a patient to take part, formal written informed consent will be sought retrospectively from the patient for continuation in the trial at the earliest appropriate time. The primary outcome measure in the trial is a patient-reported outcome measure. Therefore,

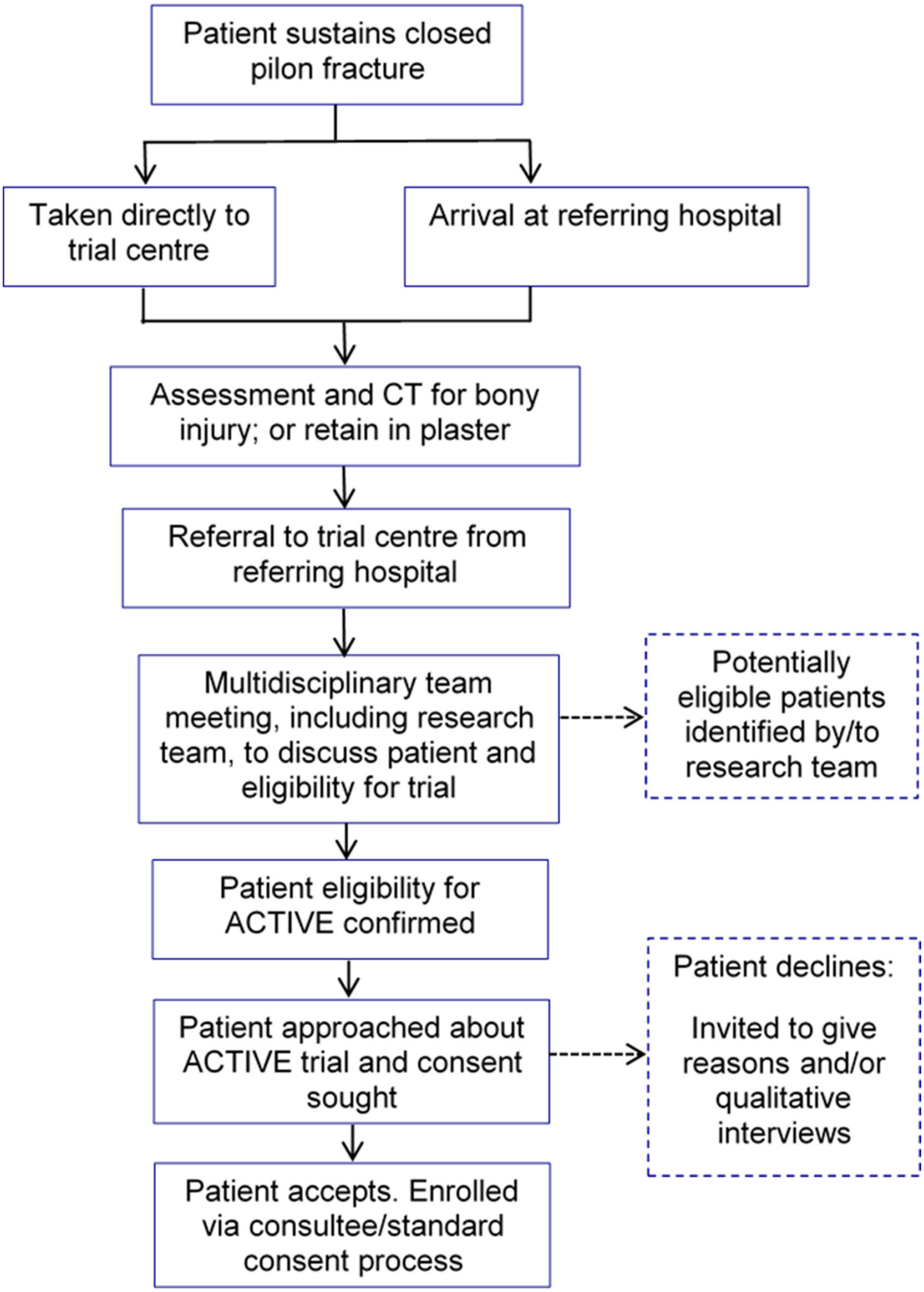

Fig. 2
Pilon fracture treatment flowchart.

participants who do not regain capacity or permanently lack capacity at three months following randomization (the time of the first follow-up data collection) will be withdrawn from the study.

Screening logs will be kept at each site throughout the trial to determine the number of patients assessed for eligibility, reasons for any exclusion, and reasons for non-consent. Additionally, screening logs will also record the type of pilon fractures seen (type C1, C2, and C3). When an eligible patient does not consent to take part, and where the patient is willing, a CRF will be completed by the research nurse (RN) to record the reason for this and their treatment plan. This information should inform efforts to optimize recruitment.

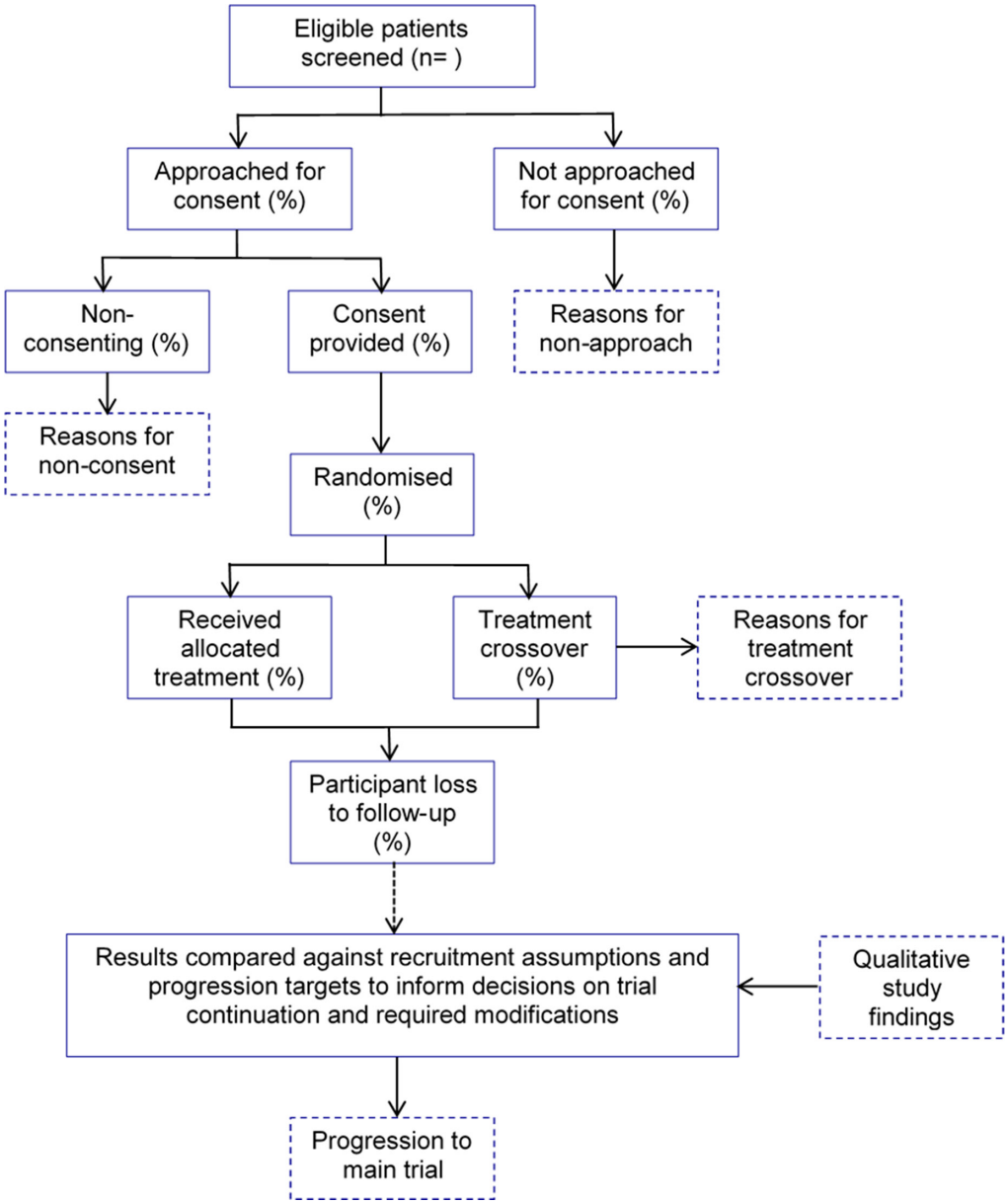

Fig. 3

Pilot study outcome data used in analysis and to inform trial continuation.

Within the UK we will explore setting up Patient Identification Centres (PICs), and a letter will be provided to trial centres to publicize the trial to referring hospitals. This is to manage treatment expectations of patients before their referral to the trial centres 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.

Internal pilot. A mixed methods internal 12-month pilot study will test assumptions about recruitment and confirm whether the trial is feasible. The internal pilot aims to: obtain robust estimates of recruitment and confirm trial feasibility; review the internal pilot recruitment targets and assumptions; provide descriptive data regarding identification, eligibility (including fracture subtype C1, C2, and C3), consent, randomization and receipt of randomized treatment, for all patients screened; and identify and describe challenges to and facilitators of recruitment as well as methods to optimize trial procedures and recruitment rates.

The proportion of eligible patients who were approached, recruited, and randomized will be calculated, and information on reasons for non-approach and non-consent will be collated. Surgeon equipoise will be monitored during recruitment by scanning reasons for exclusion during screening and reasons

Table III. List of 'expected' adverse events for the ACTIVE Trial.

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, nonunion, 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

for crossover following randomization that may reflect surgeon preferences.

A nested qualitative study will also be conducted and will include: semi-structured interviews with patients who agree to take part in the trial (n = 15 to 20) and who decline participation (n = 5 to 10); interviews with participating surgeons and trial recruiters (n = 15 to 20); and audio recordings of recruitment consultations.

All patients considered eligible to participate in the main trial will be eligible for the qualitative study. Patient interviewees will be sampled to ensure maximum variation from the cohort of interviewees who are eligible for recruitment into the trial and will be based on age, sex, and responses to the quantitative questions relating to treatment preferences and reasons for non-consent into the trial. Staff who are directly involved in patient recruitment will be invited to interview.

All interviews will be semistructured, conducted via telephone, and will follow a topic guide that was developed through discussion with the research team, Patient and Public Involvement (PPI) members, and surgeons with expertise in the area. Interviews will explore reasons for participation and non-participation, interventions, and trial processes. Particular attention will be given to exploring trial participants' and recruiters' views on randomization, treatment preferences, and the barriers and facilitators to running a full scale trial. Patient interviews will also explore the impact and acceptability of interventions and recovery in the context of patients' daily lives.

All interviews and a selection of consultation recordings (from those declining and accepting participation) will be transcribed verbatim. Data will be analyzed thematically following guidance as outlined by Braun and Clarke.[28] At the end of the internal pilot, qualitative and quantitative data will be integrated and will inform whether the study progresses from internal pilot to full study.

Treatment allocation. Following patient consent, obtained by the clinical/research team at site, and completion of baseline forms, individual patients will be randomly allocated to treatment arms in a 1:1 ratio, using computer-generated random permuted blocks of random sizes, stratified by centre. Randomization will be performed independently, either by telephone or via the internet, by York Trials Unit (YTU) using a secure web- or telephone-based randomization service to ensure concealment of the allocation sequence. The randomization service will confirm patient eligibility. Where patients have a bilateral pilon fracture, the treating surgeon will choose the worst injury to be used for the trial, prior to randomization.

The patient will be informed by the clinician of their treatment allocation. YTU will send patients and their general practitioner a letter about the trial and treatment allocation. As with many surgical trials, it is not feasible to blind patients, surgeons, or outcome assessors to their allocation. However, detection bias will be mitigated given that both groups will be receiving routinely available surgical treatments.

Data management

Data collection. Data completed by trial participants will be collected via questionnaires or in clinics as part of routine care. Data collected from the hospital will be recorded on paper CRFs by hospital staff. Each trial participant will have a unique six-digit identification number that will be pre-recorded on all CRFs.

For the qualitative study, interviews will be conducted face-to-face, via telephone, or Skype according to the preferences of each interviewee. All interviews will be recorded with permission.

Participant retention. Several methods will be employed to keep participants informed and to minimize attrition. Firstly, where patients need assistance completing questionnaires one of the study team can help them complete them over the telephone. A pre-notification letter will be sent two weeks before the follow-up questionnaire is due at three, six, 12, and 24 months, to help prime participants. A text message reminder will also be sent on the day patients are expected to receive the postal questionnaire at three, six, 12, and 24 months.[29] Two- and four-week reminders will also be sent. Where these methods fail, participants will be given the option to complete an abridged questionnaire (a minimum of the DRI and EQ-5D-5L) via telephone after the four-week reminder, which they will also be contacted about by SMS messaging. At 3, 6, and 24 month follow-up, an unconditional incentive payment of £5 will be included 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.[30] Patient newsletters will be produced during the

Table IV. Details of trial registration for ACTIVE as per the recommended World Health Organization Trial Registration Data Set

Trial registration	ISRCTN98152560
Date of registration	06/03/2018
Funder information	The National Institute for Health Research Health Technology Assessment programme (reference number: 15/130/84)
Sponsor	Hull University Teaching Hospitals NHS Trust
Scientific title	External frame versus internal locking plate for articular pilon fracture fixation: a multicentre randomized controlled trial
Countries of recruitment	England, Wales, Scotland, Northern Ireland and also exploring recruitment internationally
Health condition(s) or problem(s) studied	Closed pilon fracture of the tibia, classified AO 43 C
Intervention(s)	**Arm 1:** Internal plate fixation ('locking' plate) **Arm 2:** External frame fixation (limited open reduction and articular fixation)
Key inclusion and exclusion criteria	Inclusion criteria: ■ Patients aged ≥ 16 years; ■ 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; ■ Pathological 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
Study type	Interventional Allocation: randomized controlled trial with 1:1 allocation Primary purpose: superiority study comparing clinical and cost-effectiveness of interventions
Date of first enrolment	March 2018
Target sample size	334
Recruitment status	Recruiting
Primary outcome	DRI at 12 months
Key secondary outcomes	OMAS; DRI; health-related quality of life (EQ-5D-5L); complications (including nonunion); resource use (e.g. impact on the NHS and productivity).

DRI, Disability Rating Index; OMAS, Olerud-Molander Ankle Score.

trial to keep the participants informed and engaged with the trial.[31]

An embedded RCT will be undertaken to evaluate the effectiveness of sending a 'reply' versus 'no reply' SMS text message reminder on the questionnaire response rate at the three-month follow-up.[32]

Data management. The patient questionnaires and hospital CRFs will be designed using TeleForm software.[33] A secure electronic management system will be used to track participant recruitment and study status as well as CRF returns. Data from scanned CRFs will be verified through cross-checking against the hard copy. To maximize data quality, on their return to YTU key variables in the hospital CRFs will be reviewed by a research data administrator for completion and accuracy, who will resolve any queries with the RN at the relevant site. On their immediate return to YTU, participant questionnaires will be checked for missing data. Where this happens, a trial coordinator will call the patient to complete any missing primary outcome data, and other missing data as feasible, over the telephone. As a duty of care, free-text responses in questionnaires will be checked immediately for anything that indicates that the participant could be at risk of harm. Where this occurs, the Principal Investigator (PI) and RN will be notified via email. Following these initial checks, all CRFs will undergo a scanning process within the Teleform software, followed by second checking and validation against predetermined rules.

All data will be completely anonymized for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, once randomized, individual patients will only be identified by trial numbers.

Statistical analysis. Full analyses will be detailed in a statistical analysis plan (SAP) agreed by the independent Data Monitoring and Ethics Committee (DMEC) prior to the end of data collection. Any exploratory analyses of subgroups that are of clinical interest will be pre-specified in the SAP. This trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials.

Internal pilot. The recruitment rate and 95% confidence interval (CI) will be estimated from the data collected. Data will also be summarized for the reasons already given for doing the internal pilot. 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. Figure 3 displays how analyses from the internal pilot will contribute to progression onto the main trial.

Main trial. A CONSORT diagram will be constructed to show the flow of participants through the study and

the outcome data on screening, recruitment, and receipt of randomly allocated treatment collected. The number of participants withdrawing from the trial will be summarized with reasons where available. Baseline characteristics will be presented by trial arm both for the trial population as randomized and for those patients included in the primary analysis, i.e. those who provided a DRI score at three months, six months, or 12 months, and had data on fracture type. Statistical analyses will be on intention to treat (ITT) basis with patients being analyzed in the groups to which they were randomized. 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 summarized as means, standard deviations, medians, and ranges; categorical data will be summarized as frequencies and percentages.

The primary analysis model will be a covariance pattern mixed effect linear regression model, with DRI scores at three, six, and 12 months follow-up as the dependent variable, adjusting for randomized 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 three and six 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 timepoints 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.

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 sub-group analyses of the primary outcome, to assess the effectiveness of the different treatments across different patient sub-groups. 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 (< two days vs two to seven days vs > seven days).

Secondary continuous patient-reported outcome measures will be analyzed in a similar manner to the primary analysis model. Binary secondary outcomes of additional procedures and complications will be analyzed graphically.[34]

Cost-effectiveness analysis. The economic evaluation will assess the relative cost-effectiveness of internal plate fixation in comparison to external fine wire fixation for the treatment of Type C pilon fractures of the distal tibia. The time horizon of the analysis will be two years, as per duration of the ACTIVE trial, and will follow a NHS and Personal Social Services (PSS) 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 sub-groups defined by the statistical analysis.

The primary outcome for the economic analysis will be the additional cost per quality-adjusted life year (QALY) 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 ITT approach. Data on resource use (surgical and secondary procedure costs and equipment; information on hospital stay; primary and secondary care appointments; patient out-of-pocket costs and impact on employment), and health outcomes will be collected prospectively during the analysis using self-reported questionnaires and hospital CRFs, as previously described. 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.[35] Unit costs will be derived from established national costing sources such as NHS Reference Cost databases,[36] the Personal Social Services Research Unit (PSSRU)[37] costs of health and social care, and the British National Formulary.[38] Unit costs will be multiplied by resource use to obtain a total cost for each patient.

As previously stated, the EQ-5D-5L questionnaire will be used to measure the impact of the intervention on patient's health related quality of life. 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 timepoints and estimating the area under the curve.[39]

For the analysis, we will use regression methods following a bootstrap framework. The bootstrap's main advantage is dealing with skewed data, which often characterize 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 analyzed and handled by means of multiple imputation (MI).[40] 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 £20,000 to £30,000/QALY,[41] and also £13,000/QALY as suggested by recent research.[42,43]

If the results are deemed 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 lifetime 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. Full analyses will be detailed in a Health Economic Analysis Plan (HEAP).

Monitoring

Data monitoring. A DMEC will be established, which will be chaired by a statistician, and be independent from the funding body, Sponsor, and trial team. Their role will be to review accumulating safety, efficacy, quality, and compliance data, and advise the Sponsor (directly or indirectly) on the future management of the trial. Only the DMEC will have access to the unblinded comparative data from the study. A DMEC Charter has been agreed which they will work to.

No interim analyses for the trial are planned and there are no defined stopping guidelines. However, there will be an internal pilot study, data from which will be used by the DMEC and Trial Steering Committee (TSC) to check the assumptions about the feasibility of the trial and its continuation, particularly concerning recruitment assumptions. These data will also contribute to the final analyses.

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 potential risks associated with the surgery that participants in both groups may be affected by: infection, bleeding, and damage to the adjacent structures such as nerves, blood vessels, and tendons. Nevertheless, surgeons performing the interventions in this trial undertake these as part of routine practice and are familiar with them. The Research Governance Framework/ UK Policy Framework for Health and Social Care Research[44,45] and MRC Good Clinical Practice Guidance[46] will be adhered to, and measures taken within the trial, such as the emphasis on good practice and standardized protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits.

Adverse event management. Adverse events are defined as any untoward medical occurrence in a clinical trial participant and may be a non-serious adverse event (AE) or a serious adverse event (SAE). All SAEs will be recorded and reported by the sites to the trial team within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator (CI). 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 (S)AEs will be reported to the TSC and DMEC. For non-serious AEs, the trial team will be notified within five days of the event being known. Follow-up reports a month later will be reviewed by the CI to ensure that adequate action has been taken and progress made.

Only adverse event data related to treatment for the original injury, that are 'unexpected' will be collected, and only up until the 24-month follow-up. A list of expected adverse events that we will not report is given in Table III. 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.

Auditing. Hull University Teaching Hospitals NHS Trust will be the sponsor for the study. Data monitoring will be undertaken by the Trial Management Group (TMG), as well as the independent members of the TSC and DMEC, as previously detailed. This will be reported to the sponsor and regular progress reports will be submitted to the funding body. The study will be conducted in line with rigorous standards set out in the Research Governance Framework for Health and Social Care and the guidelines for Good Clinical Practice. The TMG will meet on a quarterly basis to review trial conduct and progress, with more frequent meetings as required.

Ethics and dissemination

Research Ethics Committee approval. REC approval was granted on 13 February 2018 (NRES Committee Yorkshire and The Humber – Bradford Leeds). Health Research

Authority (HRA) approval for the study was also granted on 13 February 2018.

Protocol amendments. Any amendments to the protocol during the course of the trial will be submitted for approval by the REC/HRA as necessary, having been agreed with the funding body, Sponsor, TSC, DMEC, and the TMG as required. Following approvals, amendments will be communicated to the participating sites for implementation in accordance with HRA approval and guidance. All amendments will be documented in the published final report to the funding body.

Consent. Written informed consent for the main trial and qualitative study will be obtained by appropriately trained research staff or clinicians at recruiting sites as per local requirements. A detailed patient information sheet for the main trial and qualitative element will be used, developed in collaboration with patient representatives, and potential risks and benefits clearly explained. Within the qualitative study, patient consent to audio-record recruitment discussions with the research team will be obtained as verbal consent, which will be audio-recorded prior to the discussion. Implicit consent will be taken from the research team by the return of completed recordings.

Patient confidentially. All participant data, including data from on qualitative interviews, will be assigned a unique coded trial ID number to maintain participant confidentiality. All paper records will be stored securely in locked cabinets in the University of York in areas with restricted access (i.e. alarmed areas, requiring key cards during working hours). After a period of time these will be transferred to a secure off-site storage facility below ground, where access is via a security controlled mineshaft with no outward markings to advertise its presence. Electronic records will be anonymous of identifiable information and stored on a password-protected server.

Recordings and transcripts from the qualitative study will be anonymized 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.

Declarations of interest. Independent members of the DMEC and TSC will be required to provide written confirmation that they have no competing interests to declare. HS is a paid consultant for Orthofix, as was NG (until the end of 2018). HS is also a paid consultant for Biocomposites and has received research grants from Smith & Nephew, BBRaun and Dermol Laboratories. NG has received educational grants from Smith & Nephew, Orthofix and Biocomposites as part of a non-profit organization organizing educational events. HS is a member of JLLR editorial board. CH and MC are members of the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Funding Board. CMcD is a member of the NIHR HTA & EME Journal Editorial Board. York Trials Unit receives funding from the British Orthopaedic Association to support grant applications. These associations and grants have not in any way influenced contribution to this study.

Access to data. Permission to access source data by study staff and for regulatory and audit purposes will be sought via the patient consent form, with an explicit explanation in the information sheet and consent discussion. External requests for data following completion of planned analysis and dissemination will be notified to the CI and Sponsor for consideration and approval before seeking confirmation from the funding body. Any data will be anonymized before secure transfer.

Ancillary and post-trial care. This is a pragmatic trial, where the trial treatments are routinely available in the NHS, and are the most frequently used treatments. Therefore any ancillary and post-trial care for the continuing treatment of a pilon fracture should be accessible to all trial participants in discussion with their clinician. If a patient is harmed through third party negligence, they may have grounds for legal action and compensation against the sponsor and/or trial team (where harm results specifically from trial participation) or the NHS (where harm results from their clinical care).

Dissemination. The trial results will be disseminated to key stakeholders and patients in various ways: in a peer-reviewed journal; production of a Health Technology Assessment (HTA) monograph; presentation at key national and international scientific meetings; generation of patient information in conjunction with patient team member for "Shared Decision Making" based on findings and update the entry on Wikipedia[47] and write the Map of Medicine[48] entry on pilon fractures management.

The full trial report will be submitted to the funding body for publication in an open access, peer-reviewed journal. 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. The trial team will work with the relevant Speciality Advisory Committees (SACs) to incorporate the findings into the training curriculum for clinicians who will undertake treatment for pilon fractures.

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. The trial protocol is being made publically available in a peer-reviewed journal.

The International Committee of Medical Journal Editors will be used to inform criteria for authorship.[49] Where criteria are not met, those who contributed to study design or drafting of research outputs will be acknowledged as contributors, with those solely involved in conducting

the trial (e.g. staff at recruiting sites) will be recognized as collaborators.

Discussion

This research will further knowledge on the clinical and cost-effectiveness of the two treatments most frequently used in routine care for the treatment of type C articular pilon fractures, a skeletal injury with one of the worst functional and health outcomes. Results will be disseminated through peer-reviewed publications and the evidence will help to inform clinical practice. As per SPIRIT recommendations for clinical trial protocols,[25] Table IV displays key items from the trial registration data set in line with World Health Organization recommendations.

Take home message

- Recent reviews of the literature and National Institute of Health and Care Excellence (NICE) treatment guidance have identified the need for robust randomized controlled trials to assess whether internal or external fixation is better for management of pilon fractures.
- The outcome of this study will directly influence clinical decision-making and health policy by informing international and UK national guidance, improve outcomes for patients, and reduce the financial burden associated with the injury.
- A systematic review by NICE identified no economic evaluations, which this study is addressing.

Twitter

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- E. Barron: Conceptualized the study, Developed the methodology, Wrote, edited, and reviewed the manuscript.
- S. Brealey: Wrote, edited, and reviewed the manuscript.
- B. Corbacho: Conceptualized the study, Developed the methodology, Wrote, edited, and reviewed the manuscript.
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ICMJE COI statement:
- H. Sharmais a paid consultant for Orthofix, as was N. Giotakis (until the end of 2018). H. Sharma is also a paid consultant for Biocomposites and has received research grants from Smith & Nephew, BBRaun and Dermol Laboratories. NG has received educational grants from Smith & Nephew, Orthofix and Biocomposites as part of a non-profit organization organizing educational events. HS is also a member of the JLLR editorial board. C. Hewitt and M. L. Costa are members of the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Funding Board. C. McDaid is a member of the NIHR HTA & EME Journal Editorial Board. York Trials Unit receives funding from the British Orthopaedic Association to support grant applications. These associations and grants have not in any way influenced contribution to this study.

Ethical review statement:
- Reasearch ethics committee approval was granted on 13 February 2018 (NRES Committee Yorkshire and The Humber – Bradford Leeds). Health Research Authority (HRA) approval for the study was also granted on 13 February 2018.