FAME: In younger adults with unstable ankle fractures treated with close contact casting, is ankle function not worse than those treated with surgical intervention?

The Fractured Ankle Management Evaluation (FAME) Trial Protocol

Short title: FAME Trial

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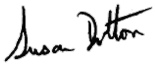

We declare no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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2. LAY SUMMARY

Background: Ankle fracture is one of the most common musculoskeletal injuries sustained in the UK. Many patients experience pain and physical impairment, with the consequences of the fracture and its management lasting for several months or even years. The broad aim of ankle fracture treatment is to maintain the alignment of the joint whilst the fracture heals and to reduce the risks of problems such as stiffness. More severe injuries to the ankle are routinely treated surgically. However, even with advances in surgery, there remains a risk of complications; for patients experiencing these, the associated loss of function and quality-of-life is considerable. Non-surgical treatment is an alternative to surgery and involves applying a cast carefully shaped to the patient's ankle to correct and maintain alignment of the joint; the key benefit being a reduction in the frequency of common complications of surgery. The main potential risk of non-surgical treatment is a loss of alignment with a consequent reduction in ankle function.

Aim: This study aims to determine whether ankle function, four months after treatment in patients with unstable ankle fractures treated with close contact casting, is not worse than in those treated with surgical intervention, which is the current standard-of-care.

Design: This trial is a pragmatic, multicentre, randomised non-inferiority clinical trial with an embedded pilot; with twelve months clinical follow-up and parallel economic analysis. A surveillance study using routinely collected data will be performed annually to five years post-treatment.

Methods: Adult patients, aged 60 years and younger, with unstable ankle fractures will be identified in daily trauma meetings and fracture clinics and approached for recruitment prior to their treatment. Treatments will be performed in trauma units across the UK by a wide range of surgeons. Details of the surgical treatment, including how the operation is done, implant choice and the recovery programme afterwards will be at the discretion of the treating surgeon. The non-surgical treatment will be close-contact casting performed under anaesthetic, a technique which has gained in popularity since the publication of the AIM trial. Eight hundred and ninety (445 per group) participants will be randomly allocated to surgical or non-surgical treatment. Data regarding ankle function, quality-of-life, complications and healthcare related costs will be collected at eight weeks, four and twelve months and then annually for five years following treatment. The primary outcome measure is patient-reported ankle function at four months from treatment.

Anticipated Impact: The 12 months results will be presented and published internationally. This is anticipated to be the only pragmatic trial reporting outcomes comparing surgical with non-surgical treatment in unstable ankle fractures in younger adults (60 years of age and younger) and as such will inform the NICE 'non-complex fracture' recommendations at their scheduled update in 2024. A report of long-term outcomes at five years will be produced by January 2027.

3. SYNOPSIS

Study Title	**The Fractured Ankle Management Evaluation – The FAME Trial**		
Internal ref. no. / short title	FAME		
Study registration	The study has been registered with the current controlled trials database under reference number ISRCTN 67007305.		
Sponsor	University of Oxford		
Funder	National Institute for Health Research Health Technology Assessment (HTA) Programme		
Study Design	Multi-centre, parallel, two arm, randomised non-inferiority clinical trial with parallel economic analysis		
Study Participants	Adult patients, aged 18 to 60 years inclusive, with an unstable ankle fracture		
Sample Size	890 (445 per arm)		
Planned Study Period	Total length of project: 46 months - set-up 5 months, 24 months recruitment, 1 year follow-up, 5 months analysis and report writing. Participants will be followed up to 1 year post-treatment. Long-term follow up will consist of annual participant follow-up and linkage to Hospital Episode Statistics databases up to 5 years post-treatment.		
Planned Recruitment period	01 Oct 2019 – 30 Sep 2021		
	Objectives	Outcome Measures	Time-point(s)
Primary	To determine whether functional outcomes at 4 months are not worse in people with unstable ankle fractures treated with close contact casting than in those treated with surgical intervention.	Olerud-Molander Ankle Score (OMAS)	4 months
Secondary	1. To quantify and draw inferences on observed differences in ankle function between the trial treatment groups at 8 weeks and 12 months post-treatment.	OMAS A-FORM Global rating of change (GRC)	OMAS at 8 weeks and 12 months A-FORM and GRC at 8 weeks, 4 months and 12 months
	2. To estimate differences in health-related quality of life	• EQ-5D-5L	8 weeks, 4 months and 12 months

	between the trial treatment groups in the first 12 months post-treatment. 3. To determine the risk of complications between the trial treatment groups in the first 12 months post-treatment. 4. To estimate the resource use, costs and comparative cost effectiveness between the trial treatment groups at 12 months post treatment.	• The Work Productivity and Activity Impairment Questionnaire (WPAI) • Adverse events • Resource use • Review of medical notes by research nurses	

	5. Long term follow-up, to be reported separately: To investigate the difference in ankle function, the risk of late adverse events and comparative cost effectiveness between the trial treatment groups within 5 years.	• Hospital Episode Statistics
		  ○ Inpatient
		  ○ Outpatient
		  ○ Emergency
		
		• OMAS
		• A-FORM
		• EQ-5D-5L
		• GRC
		• Adverse events
			5 years
			
			2, 3, 4 and 5 years

Intervention(s)	Close contact casting (non-surgical)		
Comparator	Internal fixation (surgical)		

4. ABBREVIATIONS

AE	*Adverse event*
A-FORM	*Ankle fracture outcome of rehabilitation measure*
AIM	*Ankle Injury Management*
AUC	*Area under the curve*
CI	*Chief Investigator*
CCC	*Close contact casting*
CRF	*Case Report Form*
CTRG	*Clinical Trials & Research Governance, University of Oxford*
DSMC	*Data Safety and Monitoring Committee*
EQ 5D-5L	*EuroQol 5 Dimensions 5 Levels Health Status Instrument*
FAME	*Fractured Ankle Management Evaluation*
GCP	*Good Clinical Practice*
GRC	*Global rating of change*
HES	*Hospital Episode Statistics*
HRA	*Health Research Authority*
HTA	*Health Technology assessment*
HE	*Health Economics*
ICF	*Informed Consent Form*
ID	*Identifier*
IP	*Intellectual Property*
MCID	*Minimally Clinical Important Difference*
MICE	*Multiple imputation by chained equations*
MRC	*Medical Research Council*
NDORMS	*Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences*
NHS	*National Health Service*
NIHR	*National Institute for Health Research*
OMAS	*Olerud-Molander Ankle Score*
ORIF	*Open reduction and internal fixation*
PI	*Principal Investigator*
PPI	*Patient and Public Involvement*
QALY	*Quality-adjusted life year*
R&D	*NHS Trust R&D Department*

REC	*Research Ethics Committee*
RES	*Research Ethics Service*
SAE	*Serious Adverse Event*
SHEAP	*Statistical and Health Economics Analysis Plan*
SOP	*Standard Operating Procedure*
SFQ	*Site Feasibility Questionnaire*
TIDieR	*Template for Intervention Description and Replication*
TM	*Trial Manager*
TMG	*Trial Management Group*
TS	*Trial Statistician*
TSC	*Trial Steering Committee*
WPAI	*Work Productivity and Activity Impairment: Specific Health Problem*

5. BACKGROUND AND RATIONALE

5.1. What is the clinical problem being addressed?

Every day approximately 170 people sustain an ankle fracture in the UK.[1] They may experience pain and physical impairment for several months and years after injury, either through the index injury or from complications of treatment. Prolonged work absence, chronic pain, psychological distress and later post-traumatic arthritis are all commonly reported.[2]

The aim of ankle fracture treatment is to maintain the alignment of the ankle joint whilst the broken bones heal and to reduce the risks of problems such as stiffness. Ankle fractures are variably grouped by clinicians into those in which the bones in the ankle joint are aligned and will remain so (stable) and those in which they are not (unstable).[6] The clinical and radiological features of an ankle fracture that confer instability are not resolved.[7] However, one agreed indicator of fracture instability is the presence of an injury to the posterior aspect of the ankle or posterior malleolus.[7]

Fractures that are judged to be unstable are usually treated surgically with the aim of correcting and then stabilising the alignment of the ankle bones in an attempt to ensure good ankle function once the fracture has healed.[8] Even with advances in surgery, there remains a risk of complications. Many of these complications are related to the surgical treatment – failure of bone healing (1%), wound breakdown (9.1%), metal implant failure (1.7%) or irritation from implants requiring removal (1.3%) and infection (2.7%).[3,9] For those people experiencing complications, the functional loss and decline in quality-of-life are still experienced months and sometimes years after injury.[9]

Non-surgical treatments have the key benefit of avoiding the risks of surgical complications. For example, close contact casting (CCC) involves applying a cast, carefully shaped to the patient's ankle, to correct and maintain alignment of the joint through external support. This avoids the need for incisions in the skin and implantation of metalwork, thereby reducing the risk of wound complications, infection and irritation from implants. The concern with non-surgical treatment, where the opportunity to directly and anatomically realign and fix the bones of the ankle is not realised, is that it may yield inferior outcomes compared with surgery.

However, there is increasing recognition across other orthopaedic conditions that perfect anatomical reconstruction of the bones does not necessarily correlate with improved functional outcomes.[10-12] The clinical uncertainty here lies in whether non-surgical treatment can yield similar outcomes compared with surgical treatment.

A previous large multi-centre randomised trial (Ankle Injury Management (AIM)) has investigated different health technologies in the treatment of ankle fractures in older adults.[3] The AIM trial showed that outcomes for ankle fractures in patients over 60 years of age were equivalent for patients treated with close contact casting (CCC) or surgery at 6 months and 3 years after treatment. Close contact casting involves the application of a well-fitting cast to the lower leg after the fracture has been reduced whilst the patient is under anaesthetic.

The AIM study provides clear guidance for ankle fracture care in the older patient; yet 60% of ankle fractures occur in adults less than 60 years of age.[4] The majority of these fractures in younger adults will be treated non-operatively with a standard plaster cast or walking boot. Forty per cent, however, are more severe, and currently treated with an operation; representing around 14,000 surgically treated fractures per annum in the UK.[1] Younger adults typically have a higher functional demand and may have a greater risk of developing late post-traumatic arthritis. It is reasonable to expect that treatments may yield

different outcomes in this younger population and that the findings of previous studies may not be generalisable.

Opinion is genuinely divided amongst trauma and orthopaedic surgeons in how best to manage unstable ankle fractures. All trials comparing surgical with non-surgical treatments explicitly challenge the decision to recommend surgery to a patient, the decision for which surgeons have been specifically trained. As such there are real barriers to recruitment around surgeon equipoise. However, this protocol has been developed by a wide team of professionals and patient representatives, from the British Orthopaedic Association, British Orthopaedic Foot and Ankle Society, Orthopaedic Trauma Society and Association of Trauma and Orthopaedic Chartered Physiotherapists with involvement of their memberships in a wider working group. Furthermore, the reporting of the AIM trial [3 9] has changed surgeons' views of non-surgical treatment. The UK trauma community has previously delivered on time and target for large trials comparing surgical and non-surgical treatments.[13]

This trial aims therefore to answer the research question: is ankle function at four months after treatment in people with unstable ankle fractures treated with close contact casting not worse than those treated with surgical intervention?

5.2. How does the existing literature support this research question?

A 2012 Cochrane review identified four studies comparing surgical versus non-surgical management of ankle fractures.[8] These trials were small, heterogeneous and at high risk of bias. The review concluded there was insufficient evidence to draw conclusions.

Since 2012, further trials have reported; exploratory trials by Sanders [14] and Mittal et al [15] in highly specified younger populations and the AIM trial investigating CCC as an alternative to surgery in people over the age of 60 with unstable ankle fractures.[3 9] The AIM trial found that CCC produces equivalent clinical outcomes at three years following injury and is likely to be more cost-effective compared to surgery.[9] A systematic review and meta-analysis in 2018 [16] included these and other trials comparing surgical and non-surgical treatments reporting results for the OMAS in very different populations, and the findings were inconclusive.

To our knowledge, there are no existing trials comparing CCC with surgical treatment of unstable ankle fractures in younger adults. The three ongoing studies, comparing surgical and non-surgical treatments each include only highly specific fracture variants so that the findings will not be readily generalisable to the 14,000 patients per annum treated surgically in the UK. [17-20]

5.3. Need for a trial

High quality evidence is required to determine whether the drawbacks of surgical management of ankle fracture are balanced by any improvement in functional outcomes in younger adults. The clinical and cost effectiveness of surgical management of unstable ankle fractures in younger adults was a 'Top 5 research recommendation' in the recent NICE guidance,[6] and identified as a priority at the joint Royal College of Surgeons and The National Institute for Health Research (NIHR) Research Prioritisation Exercise 2017. The NIHR Health Technology Assessment programme has commissioned a study to address this research question.

There are compelling reasons to believe that outcomes and resource use will be different in younger, working-age adults compared with older people. The risk of complications following surgical treatment in younger, fitter adults may well be lower and poor outcomes therefore less frequent; equally, productivity

losses associated with work absence may substantially influence cost-effectiveness in this working-age population.

With this substantial burden of disease, and uncertainty in the clinical and cost effectiveness of the technologies, there is a need to definitively test if non-surgical management can produce similarly acceptable outcomes as surgical management in adults aged 60 years and younger.

6. OBJECTIVES AND OUTCOME MEASURES

6.1. Primary objective

To determine whether functional outcomes at four months in people with unstable ankle fractures treated with close contact casting are not worse than in those treated with surgical intervention, which is the current standard-of-care.

6.2. Secondary objectives

The secondary objectives of this trial are:

- To quantify and draw inferences on observed differences in ankle function between the trial treatment groups at eight weeks and 12 months following treatment.
- To estimate differences in health-related quality-of-life between the trial treatment groups in the first 12 months following treatment.
- To determine the risk of complications between the trial treatment groups in the first 12 months following treatment.
- To estimate the resource use and comparative cost-effectiveness between the trial treatment groups in the first 12 months following treatment.

The objective for long-term follow-up is:

- To investigate the difference in ankle function, the risk of late complications and comparative cost-effectiveness between the trial treatment groups over five years.

6.3. Outcome measures

Table 1 describes the outcome measures being used in this trial.

Table 1: Objectives, outcome measures and time-points

Objectives	***Outcome Measures***	***Time-point(s) of evaluation of this outcome measure***
Primary Objective To determine whether functional outcomes at four months after treatment in people with unstable ankle fractures managed with close contact casting are not worse than those treated with surgical intervention.	Olerud-Molander Ankle Score (OMAS) [21]	4 months

Secondary Objectives 1. To quantify and draw inferences on observed differences in ankle function between the trial treatment groups during the first year after treatment.	OMAS [21] Ankle fracture outcome of rehabilitation measure (A-FORM) [22] Global rating of change question (GRC) [23]	8 weeks, 12 months 8 weeks, 4 months, 12 months 8 weeks, 4 months, 12 months
2. To estimate differences in health-related quality of life between the trial treatment groups in the first 12 months post-treatment.	EuroQol EQ-5D-5L [24] health-related quality of life instrument The Work Productivity and Activity Impairment Questionnaire (WPAI) [25]	8 weeks, 4 months, 12 months
3. To determine the risk of complications between the trial treatment groups in the first 12 months post-treatment.	Self-report questionnaires & medical notes: All potentially related adverse events including infection, symptomatic deep vein thrombosis, pulmonary embolus and unplanned return to theatre. Radiographs (routinely collected radiographs will be harvested): Fracture displacement, non-union, mal-union	8 weeks, 4 months, 12 months
4. To estimate the resource use, costs and comparative cost effectiveness between the trial treatment groups at 12 months post-treatment.	Review of medical notes by research nurses at all trial centres complemented by bespoke resource use questionnaires administered to patients	6 weeks, 12 months,
5. To investigate the difference in ankle function, the risk of late adverse events and comparative cost effectiveness between the trial treatment groups within 5 years.	Hospital Episode Statistics: inpatient, outpatient & emergency department databases OMAS [21] A-FORM [22] EQ-5D-5L [24] Global rating of change question (GRC) [23] Related adverse events from bespoke questionnaires administered to patients	Annually until 5 years post-treatment

7. STUDY DESIGN

This trial is a pragmatic, multicentre, randomised non-inferiority clinical trial with parallel economic analysis, with direct participant follow-up to one year, and annual surveillance extending out to five years. The trial will employ 1:1 random allocation, stratified by centre and the presence or absence of posterior malleolus fracture. If non-inferiority is demonstrated, superiority will also be investigated.

A total of 890 participants will be recruited in a minimum of 26 hospital orthopaedic departments within the UK. A member of the research team at the site will screen patients for eligibility, and when this is confirmed by a clinician, a GCP-trained member of the team will approach the patient to explain the study and gain informed consent. This consent will include permission to access data, through NHS Digital, from Hospital Episode Statistics (HES) about their hospital attendances during the 5 years following the index treatment. Participants will complete questionnaires at baseline, and follow-up questionnaires at 8 weeks, 4 months and 12 months after treatment, thereafter they will be contacted annually for a further 4 years. Five years after the date of final participant recruitment, we will collect routine hospital data through a linkage with HES (inpatient, outpatient & emergency department databases). A summary of the participant pathway can be seen in Figure 1.

Data will be collected via an instance of REDCap (Vanderbilt University Medical Center, Nashville, USA), (hosted by OCTRU, The University of Oxford, UK).[26] Baseline data, complications and review of records at the end of the trial will be directly entered onto the database by the local research team. Participants will be contacted for follow-up using email and/or SMS message prompts and invited to complete questionnaires through an online link. A schedule of email and SMS reminders and follow-up phone calls for those participants failing to complete the questionnaires will be outlined in the trial data management plan and approved by the CI and trial statistician.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Adult patients aged 18 to 60 years inclusive, who present to trauma or orthopaedic departments with an unstable ankle fracture, will be considered for entry into this trial.

8.2. Inclusion Criteria

- Patient is able and willing to give informed consent for participation in the trial, *and*
- Patient is aged 18 to 60 years inclusive with an unstable ankle fracture *and*
- who in the opinion of the treating surgeon may benefit from surgical treatment with internal fixation.

8.3. Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- The fracture is open.
- The fracture is complicated by local tumour deposits.
- The injury is an isolated fracture of the medial malleolus.
- The index injury occurred more than 14 days prior to recruitment.

- They are unable to adhere to trial procedures
- Previous randomisation in the current trial.

9. PROTOCOL PROCEDURES

9.1. Recruitment

A total of 890 participants will be recruited across a minimum of 26 sites.

The trial will be advertised to sites and potential Principal Investigators (PIs) through professional conferences and networks, with the help of the regional Clinical Research Network and through word of mouth. Our unit has a network of over 50 sites that have previously worked with us on multicentre randomised trials.

Each site will identify a surgeon to act as PI. The PI will need to utilise links with local physiotherapy departments to facilitate communication regarding the standardised rehabilitation used in the trial.

Sites will be selected based on suitability. An invitation pack which includes a Site Feasibility Questionnaire (SFQ) will be provided to potential sites. The SFQ may be completed by an individual with adequate, authoritative knowledge of the site (where a site is known to the study office through previous research enterprises the SFQ may be part-completed in advance). The PI or an appropriate deputy must confirm participation and the accuracy of any SFQ submitted to the study coordinating office in Oxford.

The coordinating team will evaluate returned SFQs to ensure a site is equipped with appropriate resources to deliver the project and meet recruitment targets. Confirmation of collaboration will be provided in writing to the PI.

9.2. Screening and Eligibility Assessment

Potentially eligible patients will be identified after referral to orthopaedic services from local emergency departments, Minor Injury Units or primary care and highlighted to the research team at the daily trauma meeting or fracture clinics. After radiographic confirmation of a fracture the local clinical team will confirm the eligibility of the individual patient to participate.

For some patients, the appropriate treatment pathway cannot be established at the first presentation due to the degree of injury to the soft tissues and/or swelling. Common clinical practice in these circumstances is to temporarily immobilise the ankle followed by a clinical assessment (with further imaging if necessary) of the injury within the first two weeks. The eligibility criteria in this trial are designed to allow for this group of patients to be included in the trial if deemed eligible within this time frame.

Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent or withdraw will be recorded. The Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will closely monitor recruitment during the pilot phase and make a decision regarding continued progress of the trial against the specified stop/go criteria. If the trial is stopped after the pilot phase, then all trial participants will be followed up as per protocol. If the trial continues into the main phase, participants from the internal pilot will be included in the final analysis.

9.3. Informed Consent

A member of the responsible clinical team will briefly highlight the study to the patient and introduce a member of the local research team. They will approach the patient and explain the trial. In order to standardise the information provided to the patients, online and written recruitment materials will be made available to local research teams. The local research team will also be able to answer any additional questions that the patient might have.

This will then lead on to an informed consent discussion and if happy to proceed the patient will provide written electronic consent. Patients will be given as much time as possible to consider the information and discuss it with relatives/carers. Qualitative research in these emergency settings has shown that patients do not feel negatively affected by the relatively short time to make this consent decision. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Prospective consent will also be sought to access the participant's personal data within the various data warehouses in the UK that hold information on patients admitted to NHS hospitals. We will use these administrative databases to source additional data for the purposes described in this protocol. For participants treated in England we plan to use admitted patient care, emergency care, outpatient care and critical care datasets within the Hospital Episode Statistics (HES) database; in Scotland, The Scottish Morbidity Register – General/Acute Inpatient and Day Case (SMR01); in Northern Ireland the Acute Episode-based Activity Statistics (EAS); in Wales, the Patient Episode Database for Wales (PEDW) derived from the Admitted Patient Care dataset. Participants will be asked to consent to the sharing of their identifiable data (NHS number, date of birth, postcode and gender) and the trial ID with NHS Digital (or equivalent) in order to link to their record. NHS Digital (or equivalent) will then provide the University of Oxford with a pseudonymised dataset containing their personal data only identified with their trial ID number. The linkage file will be destroyed by the trusted third party once the linkage is complete.

Prior to any study related procedures or data being collected participants will complete the latest approved version of the consent form. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief or Principal Investigator. Once completed, a PDF of the signed consent form will be automatically emailed to the participant. The local research team will be able to download a copy to place in the patient's medical notes. If the participant does not have access to email then a paper copy of their consent form will be provided by the local research team instead.

The consent form will include the link to the trial website so that participants will have access to all the trial information. If a participant does not have internet access a paper information sheet will be provided. The trial website will be maintained until the study archive period has reached completion. A subset of Informed Consent discussions at each site will be recorded, in order to monitor the consent process at recruiting sites and share good practice. A member of the research team will request verbal consent from the patient and the research associate before beginning the recording, and if the participant consents to recording, the discussion will begin with an oral recording of the request for consent to record, and the participant's agreement to the recording. It will be reiterated to the patients that providing consent to the recording of the consent process will not imply giving consent to participating in the trial.

9.4. Randomisation

Once informed consent has been given, the participant will be randomised by the local research team using a web-based service.

Allocations will be implemented as close as possible to the time of surgical decision-making once the participant has consented, whether this be in outpatient clinics or daily trauma meetings. Such a design most faithfully replicates real clinical practice so that the results of the trial will be as generalisable as possible to the wider NHS. This trial will test the two interventions as treatment pathways and hence be as pragmatic as possible.

The randomisation will be on a 1:1 basis, using a validated computer randomisation program managed through a secure (encrypted) web-based service by the Oxford Clinical Trials Research Unit, with a minimisation algorithm to ensure balanced allocation across the treatment groups, stratified by centre and fracture stability (defined as the presence of a posterior malleolus fracture). The minimisation algorithm will include a probabilistic element and a small number of participants randomised by simple randomisation at the start of the trial to seed the algorithm in order to ensure the unpredictability of treatment allocation.[27]

Stratification by centre will help to ensure that any centre-effect will be equally distributed in the trial arms. While it is possible that the surgeons at one centre may be more expert in one or the other treatment than those at another centre, all of the recruiting hospitals have been/will be chosen on the basis that both techniques are currently routinely available at the centre i.e. theatre staff and surgeons will already be equally familiar with both forms of intervention. Similar to the findings from other trauma trials,[28] we anticipate that each individual surgeon will only treat 2-3 participants enrolled in the trial, greatly reducing the risk of a surgeon-specific effect upon the outcome in any one centre. We will also incorporate centre as a random effect in the mixed effect primary analysis which takes into account any heterogeneity between centres. Stratification by fracture stability, specifically the presence or absence of a fracture of the posterior malleolus, will ensure that this important confounder is balanced between groups.

On randomisation of a participant the central trial office, main site contact and local study team will be notified. This will take place via an automated email as part of the randomisation process.

A paper-based randomisation system will be in place for use in emergencies, e.g. if the web-based randomisation service is not functioning, an event that is rare with this service.

9.5. Blinding

The primary outcome data will be collected from participants and entered directly onto the trial central database. It will not be possible to blind participants or those delivering the interventions.

The local research team reviewing hospital records will also not be blind to the treatment allocation. Any radiographs collected will be reviewed by an independent adjudication committee who, due to the presence of metalwork, will also not be able to perform their assessments blinded.

9.6. Description of study intervention, comparator and study procedures

Participants will be randomised to receive either surgical or non-surgical treatment. All treatments will be delivered under the supervision of a consultant trauma and orthopaedic surgeon.

9.6.1. Surgical treatment

Participants will undergo internal fixation of their fracture. The peri-operative care, for example pre-operative assessments, type of anaesthesia and the selection of antibiotics will be in accordance with local protocols. The selection of the operating position, the use of a tourniquet, approach, implants and surgical technique will be at the discretion of the treating surgeon. The specific technique and implants used by the treating surgeon will be recorded. Equally the application of any immobilising devices, such as cast or a walking boot, will also be recorded.

Participants' post-operative weight-bearing instructions will be left to the discretion of the treating surgeon, but all details will be recorded.

9.6.2. Non-surgical treatment

Participants will undergo close contact casting (CCC). Close contact casting is now an established intervention and is recommended as the primary treatment for adults over 60 years of age with unstable fractures in the current NICE guidance.[6]

In consultation with patients and patient representatives during the development of the trial protocol, and in common with the established practice for older adults based upon the non-surgical intervention tested in the AIM trial,[3] all initial manipulations and applications of CCC will take place under anaesthesia.

The method of closed fracture manipulative reduction of deformity under image intensifier guidance will be left to individual surgeons and this falls within the common contemporary skills set of trauma and orthopaedic surgeons. The anaesthetic technique will be left to the discretion of the treating anaesthetist.

The CCC will be applied to the ankle once, in the opinion of the treating surgeon, the fracture has been adequately reduced. There will be standardisation of the casting materials, cast design and application, and moulding technique, as per the AIM trial training package.[3] This technique will be revisited with clinical teams at each site with the FAME training team. In the event that an acceptable closed reduction cannot be achieved then the operating surgeon will proceed to open reduction and internal fixation (ORIF) if this is clinically appropriate. Conversion to ORIF in these circumstances, where an acceptable reduction cannot be achieved or maintained intraoperatively, will not constitute a protocol violation. Details of the reasons and the surgical technique used will be recorded.

Participants will be non-weight bearing for the duration of the CCC treatment.

The clinical follow-up schedule in the early phase will be left to the discretion of the treating surgeon. It is anticipated that some participants will require repeat applications of the CCC as the swelling around the injured ankle reduces. Subsequent applications of the CCC can be performed outside of an operating theatre, for example in plaster rooms. Advice regarding the frequency of clinical monitoring will be provided in the training sessions and rehabilitation booklet. After reapplications of the CCC repeat radiographs will be performed to confirm the reduction has been maintained.

9.6.3. Quality assurance of intervention

After discussion with patients, patient representatives and clinical experts during development of the protocol, intra-operative radiographs will be collected and assessed for technical adequacy of both interventions by an independent adjudication panel.

9.6.4. Ongoing treatment after test interventions

Clinical and radiographic monitoring of progress of both treatments will be at the discretion of the treating surgeon.

At the time a clinical decision is made to remove weight bearing and range of movement restrictions the rehabilitation materials will be delivered using standardised verbal and written and/or online instructions. A participant rehabilitation booklet has been prepared specifically for this study, with PPI input to ensure it is acceptable to participants. The booklet will be given to all participants as a printed, colour A4 booklet and may also be made available to participants online via the public website. The rehabilitation booklet includes the items below:

a. Pain: Information to aid participant understanding of the condition and its management, to counter any misconceptions and pain management strategies (e.g. use of medication)

b. Swelling: Advice on strategies to reduce swelling that include ice and elevation

c. Stiffness: A core set of exercises that replicate normal physiological movements of the ankle and stretch the main muscle groups of the lower limb.

d. Function: A core set of progressive strength exercises that target the main muscle groups of the lower limb and lower limb proprioceptive exercises.

Adhering to the TIDieR checklist for description and replication of rehabilitation interventions,[29] the initial rehabilitation intervention will be recorded on a rehabilitation CRF to capture the following information:

- Category of health care professional delivering the materials
- Grade/band of health care professional delivering the materials
- Where the materials were delivered (e.g. fracture clinic/ward/physiotherapy department)
- The duration of time (in minutes) to deliver the intervention

Training of providers will be undertaken at each site by the FAME training team in conjunction with the earlier described CCC training. Given the nature of clinical rotations that will occur on a regular basis and broader clinical team that may deliver the rehabilitation, each site will nominate a lead trainer who will be responsible for training of subsequent intervention providers. A rehabilitation booklet will be provided to the lead trainers by the trial team to standardise this process.

To increase participant adherence, there will be a further section describing the importance of recording progress and goal setting. Information will be provided on how to set goals using SMART principles. As part of this process they will be guided to include at least one of context, frequency, duration or intensity (e.g. encouraged to complete one set of exercises every day). In order to manage participant expectations of what is achievable there will be a final section informing participants of typical timescales when usual activities, such as driving, performing manual work, returning to sports, are usually resumed and points of contact if progress is not as expected.

The rehabilitation materials will only be delivered once and the time taken to deliver the intervention will be recorded on the CRF. The materials will not be tailored to the participant. Frequency and duration of exercises undertaken will be determined by the participant and they will be encouraged to record this in the relevant section of the participant rehabilitation booklet.

Further formal rehabilitation or adjunctive therapies will be left to the discretion of the treating clinician (e.g. referral to physiotherapy). Additional physiotherapy can take place in a number of settings outside of the immediate trial site; consequently this pathway will not be standardised and data will be self-reported by the participant at routine trial follow up. These data will include:

a. Where they received the physiotherapy (community, home, hospital, private).
b. Duration of the sessions.
c. Number of sessions received.
d. Method of delivery: face to face individual or group or remote telephone advice.

9.6.5. Quality assurance of standardised rehabilitation

Following site set-up the trial team will implement mechanisms to ensure treatment fidelity. This will be based on a standardised approach of evaluating fidelity:[30]

a) Direct Observations: With additional permissions, a member of the trial team will observe a subset of trial related procedures (permission will be sought from the trial participants to observe treatment sessions). An adherence evaluation form consisting of items that reflect the occurrence or non-occurrence of an event will form the basis of the assessment.

b) Self Report: Alongside this, CRFs will be collected on intervention delivery including a Rehabilitation Delivery Form. This will be completed for every trial participant by site staff.

Points a) and b) will be evaluated annually for the duration of recruitment and intervention delivery. Any issues identified will be discussed by the Trial Management Group. If issues with individual sites are not resolved following the recommendations they will be escalated to the Trial Steering Committee.

9.7. Baseline Assessments

Participants will be asked to provide their contact details as well as the contact details of up to two alternative friends or family members. Experience from numerous orthopaedic trauma trials has highlighted that collection of these additional data reduces loss to follow-up substantially.

Baseline demographic data and retrospective pre-injury functional data using the OMAS instrument [21] and A-FORM[22] will be collected. Participants will also be asked to complete the EuroQol EQ 5D-5L health-related quality-of-life questionnaire[24] to indicate their typical pre-injury health status.

9.8. Clinic Visit

Participants will usually attend at least one visit to the orthopaedic or trauma clinic after their initial treatment as part of standard care. During this visit, approximately 6 weeks post-treatment, the clinical team will perform a clinical assessment and standard radiographs will be taken. The research team will record any early complications that have occurred. The research team will transfer redacted radiographs taken intra-operatively and in the time since their index treatment to the central office, where they will be assessed by an independent adjudication committee.

9.9. Remote follow-up (8 weeks, 4 & 12 months and 2-5 years)

At 8 weeks, 4 months and 12 months after treatment, participants will be contacted by the central study office and invited to complete the OMAS, A-FORM, , EQ 5D-5L, patient reported experience (resource use and GRC) and WPAI questionnaires.

At 12 months participants will additionally be asked how they felt about being in the study in the Post-assessment questionnaire.

In a long-term follow-up, to be reported separately, at 2, 3, 4 and 5 years after treatment participants will be contacted by the central study office and invited to complete the OMAS, A-FORM, EQ 5D-5L, adverse events and GRC questionnaires.

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

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

9.10. Review of medical notes

At 12 months, the local research team at each centre will review hospital records for the trial participants and collect information on any visits and/or admissions related to the index fracture. These may include details of rehabilitation sessions offered at the treating centre and other outpatient care, including type of clinic visited and frequency, treating health care staff, and whether first appointment or routine follow-up; accident and emergency visits; and day-case and inpatient readmissions to hospital, reason for readmission, procedures and tests performed, and days admitted to various wards.

9.11. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the study at any time, without giving reasons, and without prejudicing their clinical care.

Participants will **not** have the option to withdraw the data collected up until the point of withdrawal, as the data will be required for the intention-to-treat analysis and safety analysis. The options for withdrawal will be explained clearly in the Participant Information Sheet. The type of withdrawal and reason for withdrawal, if the participant is willing to provide one, will be recorded in the withdrawal CRF.

9.12. Definition of End of Study

The main analyses will be completed and reported after one year follow-up of the last participant. A planned long term follow-up study will be continued to the date of the last five year follow-up of the last participant. The end of study is defined as the 5-year follow-up of the last participant and once all queries have been resolved.

10. SAFETY REPORTING

This is a low risk, pragmatic trial where both of the trial interventions are in common use. In light of this, we do not anticipate many serious adverse events (SAEs) associated with either treatment. All adverse events will be reviewed by the local Principal Investigator and, submitted to the FAME central office if they fall into the SAE categories defined below.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect
- 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.

10.2. Reporting Procedures for Serious Adverse Events

For the purpose of safety recording for this trial, only unexpected serious adverse events (SAEs) potentially related to the intervention will be reported immediately to the Trial Team. When the local research team becomes aware of an unexpected SAE in a trial participant, the Principal Investigator (PI) will review the SAE locally and make a decision about the relatedness of the event to the intervention. If the PI assesses the SAE as potentially related and unexpected, the details of the event will be entered on an SAE reporting form on the database, and the research team will notify the trial team via email within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator or delegate. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) within 15 days. All such events will also be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

10.3. Reporting Procedures for Adverse Events not defined as serious

Adverse events that are unrelated to the intervention or treatment will not be reported.

Adverse events (AEs) that are foreseeable in the treatment of these fractures, and are not defined as SAEs, do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires.

Other adverse events, foreseeable or unforeseeable, that are not in this list, will not be reported.

Foreseeable, related AEs include the following:

(a) Related to CCC only:
- loose cast or tight cast requiring reapplication
- failed closed reduction
- pressure ulcer
- plaster saw laceration

(b) Related to surgical treatment only:
- surgical site infection
- failed fixation
- prominent implant
- wound dehiscence
- vascular injury

(c) Related to both treatments:
- revision surgery, defined as unplanned return to theatre
- symptomatic deep venous thrombosis
- symptomatic pulmonary embolus
- compartment syndrome
- nerve palsy
- complex regional pain syndrome
- pain/irritation/itchiness from cast

11. STATISTICS AND ANALYSIS

All available data from both treatment arms will be used in data analysis. Reporting of the results will be in accordance with the CONSORT statement [31] using the extensions for non-pharmacological treatment interventions and patient-reported outcomes. Baseline demographic data will be summarised to check comparability between treatment arms. Standard statistical summaries and graphical plots will be presented for the primary outcome measure and all secondary outcome measures. Differences between treatment groups will be assessed on both an intention-to-treat and per protocol basis, using a normal approximation for the OMAS score, [21] at four months post-treatment, and at additional time-points.

11.1. Statistical & Health Economics Analysis Plan

A statistical and health economic analysis plan (SHEAP) with full details of all analyses will be drafted early in the trial and finalised prior to primary outcome analysis. The SHEAP will be reviewed and will receive input from the Trial Steering Committee (TSC) and the Data Safety and Monitoring Committee (DSMC). Any changes or deviations from the original SHEAP will be described and justified in the protocol, an updated SHEAP, final report and publications as applicable, depending on the timing of the changes. Interim analyses of efficacy outcomes are not planned and will be performed only where requested by the DSMC. Following a blinded analysis of the data, undertaken prior to the final data-lock, the per-protocol population will be finalised and the SHEAP updated. It is anticipated that all analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages.

11.2. Sample Size Determination

The primary clinical outcome is OMAS at 4 months. Previous studies have demonstrated a minimally clinical important difference (MCID) of 10 points, [3 32] which is in accordance with expert opinion (for scales scoring 0-100) and statistical convention. [3 33] We have selected a standard deviation (SD) of 21.8 based on the largest published RCT studying the OMAS within six months of surgically treated ankle fracture. [3] Although AIM included participants aged over 60 years we are not expecting the variability in OMAS in participants aged 60 years and younger to be different. A non-inferiority margin of 5 points has been chosen. This is half the MCID (one method of choosing the non-inferiority margin) and this has been discussed with clinical experts who felt that this would provide enough evidence to change clinical practice, whereas using 6 points (as AIM used for its equivalence margin) would be less convincing in this patient population.

800 participants providing data at four months will provide 90% power and 2.5% (1-sided) significance to detect whether non-surgical treatment for the treatment of unstable ankle fractures is non-inferior to surgical treatment using a non-inferiority margin of -5 points on the OMAS score at four months. Allowing for 10% loss to follow-up, this yields an overall target of 890 participants (445 per arm). [34] Essentially the lower 95% confidence interval of the treatment difference is assessed against the non-inferiority margin

of -5 points and if it lies above this then the trial will be assessed as non-inferior. If non-surgical management is found to be non-inferior to surgical management of unstable ankle fractures then superiority will also be tested at 2.5% (1-sided) significance (the equivalent of comparing the lower 95% confidence interval against Zero rather than -5 points).

11.3. Analysis populations

The per protocol (PP) population will include all patients who received their allocated treatment and did not have any major protocol deviations with available data at all time-points up to and including 12 months. Major protocol deviations will be pre-specified in the Data Management Plan and SHEAP and finalised following a blinded review of the data prior to the primary outcome analysis data-lock.

The Intention-to-Treat (ITT) population will include all participants with available data at all time-points up to and including 12 months in the randomised groups to which they were allocated regardless of which treatment they actually received.

11.4. Description of the Statistical Methods

In non-inferiority trials we want to show that the new treatment is not clinically worse than the active control and therefore the interest is one-sided. The new treatment may be better than the control, but it is at least non-inferior to it. We define a non-inferiority margin (Δ_T), which is the maximum difference we are prepared to tolerate in a given direction that the new treatment is not to be considered clinically inferior to the well-established standard treatment. The null hypothesis is therefore that a difference of greater than Δ_T exists in favour of the standard treatment (H_0: $\Delta \leq -\Delta_T$) (Δ defined as the difference between treatment and control (T-C)) and the trial is targeted at disproving this in favour of the alternative that the new treatment is non-inferior (H_A: $\Delta \geq -\Delta_T$). This will be assessed by creating a 95% confidence interval which should be entirely above the non-inferiority margin for the new treatment to be declared non-inferior. FDA regulations recommend that both a treatment received (per protocol) and intention to treat (ITT) analysis is performed aiming to demonstrate non-inferiority. Use of the ITT approach as in a superiority trial sometimes increases the chance of falsely claiming non-inferiority. Therefore, the primary analysis will be undertaken on the per-protocol population, where only those patients who received their allocated treatment will be analysed and those that do not will be excluded from the analysis. A secondary analysis will be undertaken on the ITT population where all randomised patients will be analysed according to their treatment allocation.

The result of the analysis for the primary endpoint should be one of the following:

- The confidence interval for the difference between the two treatments lies entirely above the non-inferiority margin (-ΔT), so that non-inferiority may be concluded with only a small probability of error.
- The confidence interval includes points below the non-inferiority margin, then there is a possibility that the new treatment is inferior to the control and non-inferiority cannot be safely concluded.
- The confidence interval is entirely above zero, indicative of a treatment effect, then superiority of the new treatment can be concluded within a small probability of error.
- The confidence interval is entirely below the non-inferiority margin, indicative of the new treatment being clinically inferior to the control.

As well as assessing if non-inferiority (and superiority) is demonstrated, sensitivity analyses will be undertaken to assess a range of potential biases that could have resulted from loss-to-follow-up, protocol deviations, or withdrawal (including mortality). Numerical and graphical summaries of all data will be

compiled including descriptions of missing data at each level. Estimates of treatment effect will be reported with 95% confidence intervals and a figure showing confidence intervals and margins of non-inferiority will also be presented. The main analytical methods will be generalised linear models and all analyses will adjust for important baseline covariates to maximise precision.

The OMAS score [21] at four months is the primary outcome in this study and will be compared between treatment groups as the dependent variable in a mixed-effects linear regression model for the primary analysis with adjustments for stratification factors and baseline (pre-injury) OMAS score. [21] A random effect will be included to account for any heterogeneity in the response due to recruitment centre. Fixed effects will be included to adjust for participant age and gender and fracture stability. The treatment difference will be based on the estimate of adjusted means and 95% confidence intervals. A fully adjusted analysis will also be undertaken adjusting for additional important prognostic variables using the same methods and an unadjusted analysis will also be undertaken using Analysis of Covariance adjusting for baseline OMAS scores only. [21] Supplementary analyses will also be conducted for the OMAS score [21] using the area under the curve (AUC) summary statistics. [35]

Where severe departure from normality is identified, the first approach will be data transformation. If the data cannot be transformed to normality then the Mann-Whitney U test will be used (in this case, no further adjustments will be made). The primary focus will be the comparison of the two treatment groups of participants, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions. The adjusted analysis using the per-protocol population will be considered the primary analysis to determine non-inferiority and superiority (if shown to be non-inferior) with the additional analyses, including using the intention-to-treat population, providing supporting evidence. Secondary clinical outcomes will be similarly analysed using mixed effects regression, using logistic regression for binary data and linear regression for continuous data.

11.5. Description of the Health Economics Methods

A prospective economic evaluation at 12 months, conducted from an NHS and personal social services perspective, will be integrated into the trial design. All economic analyses will be performed both on a per-protocol and on an intention-to-treat basis, as per statistical analyses of outcomes. Given that this economic evaluation will be conducted alongside a non-inferiority trial, per protocol estimates may retrieve more conservative estimates. The economic evaluation will estimate the difference in the cost of resource inputs used by participants in the two arms of the trial, allowing comparisons to be made between the surgical and non-surgical treatment of unstable ankle fractures in adults aged 60 years or less and enabling costs and consequences to be compared.

Consequences of interest will be quality-adjusted life years (QALYs) at 12 months and clinical primary outcome of the OMAS score[21] at four months, but all other secondary outcomes will also be reported in a cost-consequences table and follow NICE guidelines.[36] Given the importance of returning to work and usual activities to the younger patients with ankle fracture, we will separately report productivity losses from paid and unpaid work and need of informal care.

Resources used to deliver the treatment in both arms will be valued using a macro-costing approach when possible, using department of health and social care reference costs for secondary care resources[37], unit costs for health and social care for community resources[38], average weekly earnings for productivity losses [39]and patient self-reported expenses. Costs will be reported grouped by secondary care resource use, community-based resource use (including primary and social care) and productivity losses (including lost time off-work, leisure and informal care). The aggregate health and social care at 12 months will also be

reported. Costs and QALYs will be estimated using regression analyses controlling for baseline scores and trial stratification variables.

In the economic analyses, given the number and nature of resource use data collection methods and time-points, we expect the amount of missing data to be considerable. Multiple imputation methods will be used to impute data both in the per protocol and ITT analyses. We will jointly input cost categories and health outcomes if computationally feasible and supply imputed primary outcome data estimates for the statistical analysis.

The results of the economic evaluation will be reported in cost consequences tables and in cost-effectiveness planes. We will derive incremental net monetary benefit statistics using the NICE recommended thresholds of £20,000 and £30,000 per QALY but also a lower threshold of £10,000/QALY. We will use non-parametric bootstrap estimation to derive 95% CIs for mean cost differences between the trial groups and to calculate 95% bootstrapped CIs for incremental net monetary benefit statistics.

A series of sensitivity analyses will be undertaken to explore the implications of uncertainty around the costing and methodological assumptions on the incremental net monetary benefit statistics and to consider the broader issue of the generalisability of the study results. One such sensitivity analysis will involve adopting a societal perspective for the economic evaluation, which will incorporate direct costs to trial participants, informal care provided by family and friends and productivity losses.

11.6. Long term data analyses

These analyses will not be reported in the initial publications of the trial results (limited to one year follow-up) but will be reported in a separate publication at the end of the five year follow-up period

The long-term follow-up data will be collected to achieve three objectives: firstly, longer-term clinical effectiveness of the two treatments under investigation will be assessed; secondly, we will validate patient-reported hospital healthcare use collected during the trial against data collected from HES, and finally, we will assess the 5-year cost-effectiveness of CCC compared with surgery.

For the validation of hospital healthcare use, we will restrict the analysis to those trial participants who give consent to our accessing their hospital records. A detailed characterisation of the consenting and non-consenting groups will be undertaken in terms of basic demographics and primary/secondary trial outcome measures to provide context for the longer-term analysis restricted to consenting participants. HES inpatient, outpatient and A&E attendances during the 12-month trial duration will be compared to what was reported by patients through CRFs. Relevant HES records will be identified using OPCS-4 codes corresponding to the CRF wording used for collection of hospital resource use. As the validation will compare the number of attendances to the various hospital services, missing data will not be a problem as a record of hospital attendance in HES will be the only marker required to identify the use of resources.

For the cost-effectiveness analysis, an economic model will be built and populated with observed hospital costs derived from HES (including late complications), outcome data (OMAS and EQ-5D, separately for the cost-effectiveness and cost-utility analyses, respectively) collected annually from trial participants, and plausible assumptions on the extrapolation of trial findings for all other model inputs. As the analysis will be conducted based on costs and outcomes for trial participants, the model will be used to produce results for alternative scenarios or sensitivity analyses on the assumptions and extrapolation of specific parameters collected only during trial duration.

The 5-year long-term patient-reported outcomes (OMAS and EQ-5D) will be analysed using a multilevel mixed-effects model using repeated measures over time nested within participants as described for the

primary (short-term) outcomes. The model will include centre as a random effect and age, gender and fracture instability and other important prognostic factors as fixed effects as planned for the short-term outcomes. This will enable us to include all available data from all time-points. Trends over time will also be examined and if appropriate time by treatment interactions will be added to the model. In addition, an AUC summary statistics will be compared between the two interventions.

Missing data can be expected for both outcome measures at any time point they are collected as well as for resource use questions during the trial. As indicated above, hospital resource use observed in HES will not carry a risk of missing data, but OMAS and EQ-5D will. We will use multiple imputation by chained equations (MICE) for any unanswered question in these. Missing data will be imputed simultaneously for both outcome measures at each point they are collected using linear regression models. Independent variables in the imputation models are likely to include baseline and subsequent values of both outcome measures, use of resources, gender, age at randomisation, and trial arm. Imputations will be run separately by treatment arm and a total of 20 sets of imputed values generated and estimations produced accounting for uncertainty due to imputation.

11.7. Decision points

This trial will have one decision point, at the end of the pilot phase.[40] The pilot phase represents the first nine months of recruitment during which it is expected that a minimum of nine sites will be open to recruitment. The decision with regards to the continuation of the trial will be based on the total recruitment across recruitment centres. The stop-go criteria are given in Table 2. If recruitment fails to reach 100 participants by the end of the pilot phase (nine months after trial opening), the DSMC may recommend that the trial is terminated.

Table 2: Stop/Go criteria for main trial

	Actual recruitment		
Target = 200	**<100 participants**	**100-150 participants**	**>150 participants**
Recruitment rate (per centre per month)	**1.0**	**2.0**	**3.0**
Stop-go criteria	**Recruitment not feasible; decision not to proceed**	**Review recruitment strategies. Report to TSC. Continue but modify & monitor closely**	**Recruitment feasible; proceed with study**

11.8. The Level of Statistical Significance

One-sided 2.5% significance will be used for the non-inferiority comparisons. For superiority comparison and secondary outcome analyses 5% (2-sided) significance will be used.

11.9. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data, e.g. due to withdrawal, protocol violation or patient loss to follow-up will be summarised and patterns analysed. The primary analysis method is reasonably robust to missing at random data where

all available data at all time-points is utilised.[41] Sensitivity analyses will assess departures from the missing at random assumptions using multiple imputation techniques if appropriate.

11.10. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any proposed changes from the original SHEAP will be included in an updated protocol, updated SHEAP and/or reported in the final report as appropriate to the timing of the changes.

12. DATA MANAGEMENT

The Case Report Forms will be designed by the trial manager in conjunction with the trial management team, statisticians and economists. Full details will be in the Data Management Plan.

Whenever possible, data will be collected in electronic format with direct entry onto the trial database, including the collection of documentary evidence of consent. Electronic data collection has the major advantage of building "data logic" and "edit checks" into forms, minimising missing data, data input errors and ensuring the completeness of consent forms. All data entered will be encrypted in transit between the participant's web browser and server. All identifiable information will be held on a server located in an access controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis.

Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the public to see on the study website.

Paper forms with identifiable data will not be collected. Identifiable data will be limited to contact details and will be accessed separately from the outcome data obtained from/about the participants and managed within the rules of the clinical database system. In all other data, participants will be identified by a trial ID only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All electronic data will be retained for at least three years after publication of the trial. Contact details will be retained until the long term follow up is complete (5 years after treatment). The data from consent forms (in most cases the consent will be given electronically) will be retained for one year after end of the long-term follow-up.

We will collect the NHS number of participants, which we will store securely until 1 year after the end of the 5-year follow-up of the trial. This will enable us to collect long-term (5 year) outcomes using linkage to routinely collected healthcare data to identify interventions on the ankle recorded within routine hospital procedural databases. Audio recordings of consent taking of a subset of trial participants will be electronically transcribed by a member of the central trial team, and the anonymised transcriptions stored on secure servers at the University of Oxford, identified by a trial ID and/or initials only.

12.1. Source Data

Participant questionnaires will be entered online directly into the trial database, which will be the source data. Full details will be recorded in the Data Management Plan.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

Trial data will be collected and managed using REDCap electronic data capture tools hosted at OCTRU, University of Oxford.

REDCap (Research Electronic Data Capture) [26] is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Wherever possible, trial data will be entered directly into the trial database by site staff or participants. No paper forms will be provided to participants for data collection. Data captured during phone calls to participants and trial data completed on paper forms by local site staff will be entered into the trial database by suitably trained central office staff. Full details will be recorded in the Data Management Plan. The participants will be identified by a unique trial specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. sending follow-up reminders for online form completion).

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and OCTRU standard operating procedures (SOPs).

A Monitoring Plan which involves a risk assessment will be developed according to OCTRU's SOPs. The monitoring activities will be based on the outcome of the risk assessment and may involve central monitoring or site monitoring.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens to recruitment and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Quality control procedures will be undertaken during the recruitment and data collection phases of the study to ensure research is conducted, generated, recorded and reported in compliance with the protocol, GCP and ethics committee recommendations. The Chief investigator and the Trial manager will develop data management and monitoring plans.

13.3. Trial Oversight

The trial will be conducted in accordance with the Medical Research Council's Good Clinical Practice (MRC GCP) principles and guidelines, the Declaration of Helsinki, OCTRU SOPs, relevant UK legislation and this Protocol. GCP-trained personnel will conduct the trial.

13.4. Trial Management Group

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by a Senior Trial Manager. This will be overseen by the Trial Management Group (TMG), who will meet monthly to assess progress. A Patient and Public Involvement (PPI) representative will be an integral member of the TMG. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

13.5. Trial Steering Committee

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with NIHR HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives.
- review at regular intervals relevant information from other sources.
- consider the recommendations of the DSMC.
- inform the funding body on the progress of the trial.

The TSC will include at least one PPI representative as an independent member.

13.6. Data Safety and Monitoring Committee

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. The DSMC will advise the TSC on continuation of the trial at the end of the pilot phase. They will also review accruing data and summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.2. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and other study materials will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.3. Reporting

The CI will submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties. The CI will submit progress reports to the funder at the end of each calendar month and at 6 monthly intervals.

14.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a trial ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. The authorisation functionality within the data collection system will be utilised to ensure that identifiable data can only be accessed by appropriate members of the trial team. All documents will be stored securely and only be accessible to study staff and authorised personnel. The study will comply with the General Data Protection Regulation and the Data Protection Act (2018), which requires data to be de-identified as soon as it is practical to do so.

14.5. Expenses and Benefits

Participants will not undergo any hospital visits in addition to normal care, therefore no expenses will be payable.

14.6. Transparency in research

The trial is registered as ISRCTN 67007305.

The trial team undertakes to keep trial data up to date and to make the results publicly available.

15. FINANCE AND INSURANCE

15.1. Funding

This study is funded by the National Institute for Health Research Health Technology Assessment (NIHR127273).

15.2. Insurance

The Sponsor has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – which would operate in the event of any participant suffering harm as a result of their involvement in the research. Standard NHS cover for negligent harm is in place for NHS procedures. There will be no cover for non-negligent harm.

15.3. Contractual arrangements

A contract will be drawn up between the Department of Health and the University of Oxford. Further collaboration agreements will be completed between the University of Oxford and the Universities of Bristol and Warwick, University Hospitals of Leicester NHS Trust and South Tees Hospitals NHS Foundation Trust.

16. PATIENT AND PUBLIC INVOLVEMENT

We have been working with and listening to the views of patients in this area for many years. However, as well as this informal contribution, a series of formal qualitative interviews with patients and clinicians were performed in the development of the trial application.

The views of our patient representative will be used to inform and refine the trial interventions and processes, including recruitment of patients. We expect this to be integral at all stages of the project, including research design, management of the research and dissemination of findings.

The TSC and TMG will each include at least one PPI member who will be involved in discussion and decision making. We will maintain communication with the TSC members between meetings (TSC meetings are normally annual) with emails and newsletters.

The patient perspective has been key in the development of the trial protocol and will ensure the acceptability of the interventions and participation. We anticipate broad interest in the results, due to the high frequency of this injury, and we expect that our PPI members will assist in shaping our message for a lay audience.

17. PUBLICATION POLICY

The study monograph will be prepared for the funder by the trial management team upon completion of the trial. The Investigators will be involved in reviewing drafts of manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. No patient identifiable information will be contained in any form of dissemination of study results.

Dissemination will be via traditional and novel methods:

- Conference: Traditional conference dissemination will focus on presentations to include the key professional stakeholders (orthopaedic surgeons, physiotherapists, occupational therapists and trainees in orthopaedic surgery).
- Publications: Key outputs will be published in high-impact journals with publicity sought in other professional journals. We will ensure that plain English summaries are published alongside the full paper, along with links to other digital media on the trial website to explain the trial result in an accessible format. Given the frequency of the injury, this is also likely to be of interest to international press outlets. A report of long-term outcomes at five years will be produced by Jan 2027.
- Policy Makers: We will ensure the development of links with key organisations such as NICE, NHS Information Centre and NHS England to contribute to and capitalise on their networks. Most importantly the outputs will directly contribute to the NICE non-complex fracture recommendations at their scheduled update.
- Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (e.g. NDORMS twitter) with an explainer video and infographic. We will seek to engage the NHS Dissemination centre.

18. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of Intellectual Property (IP) generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

19. ARCHIVING

Documents and electronic systems will be archived as per the appropriate SOPs as prepared by the Oxford Clinical Trials Research Unit.

20. PROJECTED PROJECT TIMETABLE AND MILESTONES

This is a 46 months study starting in May 2019 and reporting in March 2023. The trial will thereafter be extended to January 2027 when results of the five year long-term follow-up will be reported. The planned trial timetable is shown below, with key milestones indicated and the responsible parties identified.

Table 3: Project timetable and milestones

Month	By date	Activity	Milestone	Responsibility
0-5	May 2019	Start study	1st TSC/DSMC meeting	CI/TM
	Jun 2019	Complete study set-up	Protocol and CRF approval sponsor and REC	TMG
	Sep 2019	Achieve CTU 'Green Light'	CRF final version	CI/TS/TM
5-14	Oct 2019	Start pilot recruitment	1st trial site open for recruitment	CI/TM
	Jan 2020		All 9 pilot sites open for recruitment	CI/TM
	Jun 2020	End pilot recruitment	TSC make recommendation to progress to full trial	CI/TSC
14-20	Jul 2020	Start recruitment at main trial sites	1st main trial site open for recruitment	CI/TM
	Dec 2020		All 26 main sites open for recruitment	CI/TM
14-29	Sep 2021	Complete recruitment	890 patients recruited	
30-41	Sep 2022	Complete follow-up all sites	All patients completed 12 months follow-up and review of medical records performed	

42-46	Dec 2022	Analyses		HE/TS
		Reporting		TMG
	Feb 2023	Main trial phase close-down	Final TSC/DSMC meeting	CI/TM
47	Mar 2023		HTA report	TMG
53	Sep 2023	Long term follow-up	All patients completed 2 year follow-up	CI/TM
65	Sep 2024		All patients completed 3 year follow-up CI/TM	CI/TM
77	Sep 2025		All patients completed 4 year follow-up	CI/TM
89	Sep 2026		All patients completed 5 year follow-up	CI/TM
91	Nov 2026	Analysis	Analyse clinical effectiveness and health economics data	TS/HE
93	Jan 2027	Report	Manuscript submission	TMG

***CI** Chief Investigator, **DSMC** Data Safety and Monitoring Committee, **HE** Health Economics, **TS** Trial Statistician, **TM** Trial Manager, **TMG** Trial Management Group, **TSC** Trial Steering Committee.*

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22. FAME PARTICIPANT PATHWAY

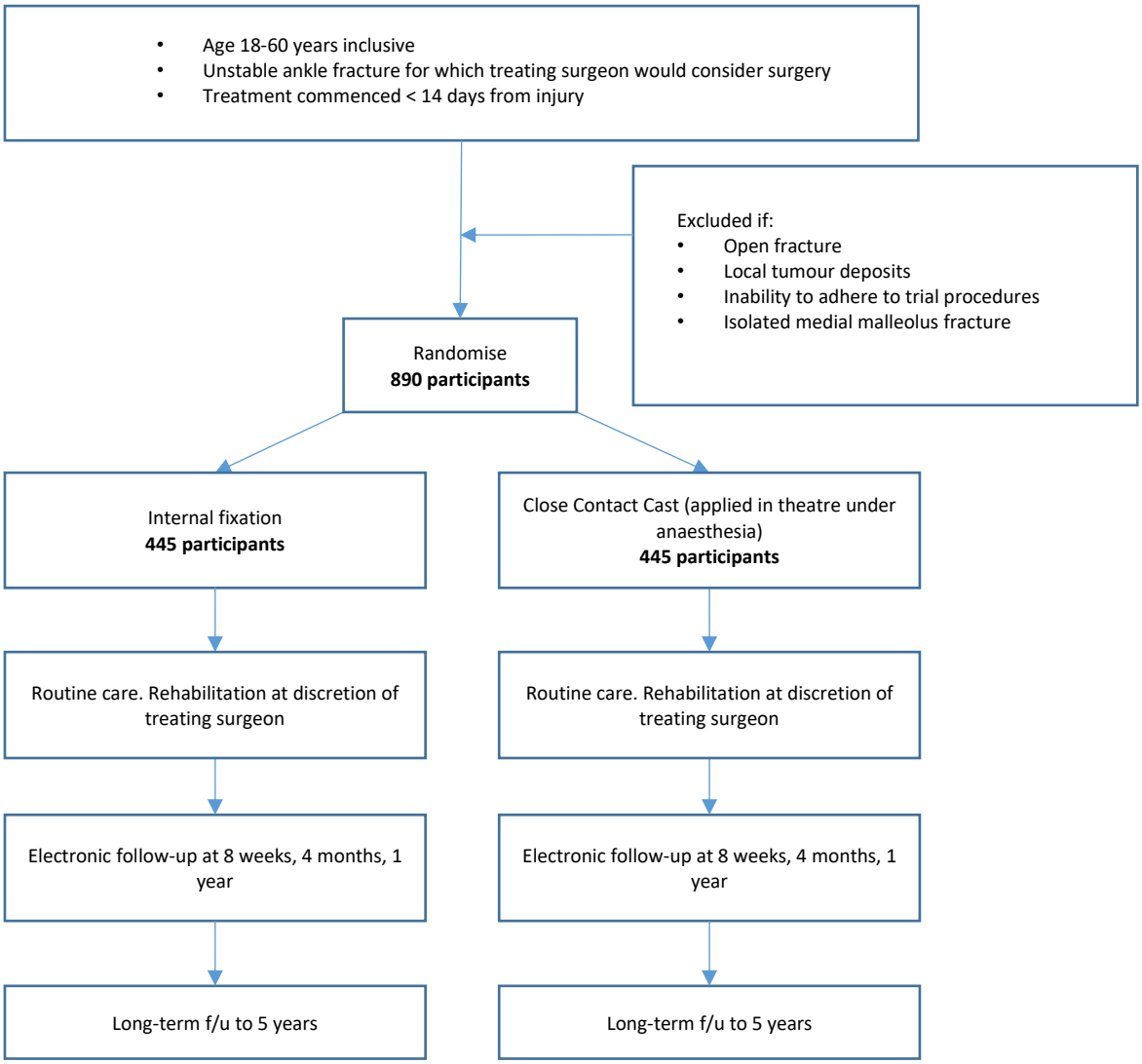

Figure 1: FAME participant pathway

23. HISTORY

Amendment No.	***Protocol Version No.***	***Date issued***	***Author(s) of changes***	***Details of Changes made***
N/A	*1.0*	*08Jul2019*	*N/A*	*None as this is the first issue*
AM01	*2.0*	*Xxxxxxxxxx*	*S Wagland*	*Section 1 Key contacts: Correction to DSMC membership;* *Section 3 Synopsis, Section 6 Objectives and outcome measures and Section 9.9 Remote follow-up: corrections to time-points of questionnaires;* *Section 9.3 Informed consent: to specify that the participant is asked for their gender, not sex;* *Section 9.4: inclusion of a reference to an emergency paper-based randomisation procedure;* *Section 9.6.4, to refer to the Participant rehabilitation booklet;* *Section 9.12: clarification of the date of End of study;* *Section 10: clarification of SAEs, AEs to be reported, and complications to be collected* *Section 12: clarification on storage and access of personal identifying data;* *Section 12.3 Clarification that no paper forms will be provided to participants;* *Inclusion of sections 14.6, Transparency in research, and 18, Intellectual property, to be compliant with new sponsor Protocol template version v15.0;* *Minor corrections and clarifications.*