PROTOCOL

Study Title

AIM: Ankle Injury Management

A pragmatic multi-centre randomised controlled trial comparing close contact casting technique (CCC) to open surgical reduction and internal fixation (ORIF) in the treatment of unstable ankle fractures in patients over 60 years

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1. AMENDMENT HISTORY

Aim Trial Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1	August 2009	Keith Willett	• Original protocol
Non-substantial Amendment No.1	2	18 February 2010	Keith Willett	• Minor clarifications
Substantial Amendment No.1	3	25 May 2010	Keith Willett	• Removal of 10 day ASEPSIS assessment • Addition of EQ-5D at baseline 'with injury' • Addition of health economic questions at 6 weeks
Non-substantial Amendment No.4	4	11 November 2010	Keith Willett	• Minor clarifications
Non-substantial Amendment No.5	5	16 August 2011	Keith Willett	• Update name of service used to match, flag and trace patients (p.15) • Update x-ray processing (page 29)
Substantial Amendment No.4	6	10 April 2013	Keith Willett	• Change to the follow up time frame. Now at least two years (rather than at five years).
Non-substantial Amendment No.9	7	24 January 2014	Keith Willett	• Statistical section in line with analysis plan • Clarify x-ray review

2. SYNOPSIS

Study Title	AIM: Ankle Injury Management
Study Design	A pragmatic, multi-centre, individually randomised controlled equivalence study with parallel prospective economic evaluation
Study Participants	Men or women over 60 years with displaced unstable fracture of the ankle and are suitable for anaesthesia for both ORIF and CCC
Number of Participants	620
Planned Study Period	5 years
Primary Objective	To determine if the application of the close contact casting technique (CCC) for displaced ankle fractures in older adults results in an equivalent outcome compared to the standard care of open surgical

	internal fixation (ORIF) in terms of function, complications, quality of life and patient satisfaction with treatment.
Secondary Objectives	An economic evaluation running in parallel to the study which will consider the costs of the two treatments to (i) the NHS, and (ii) the broader societal perspective including to the individual and their family.
Primary Outcome	6 months - patient reported functional outcome score based on the Olerud & Molander Ankle Score
Secondary Outcomes	6 weeks - assessments of function, complications, quality of life and patient satisfaction with treatment 6 months - assessments of function, complications, quality of life and patient satisfaction with treatment, cost effectiveness Extended follow up (at least 2 years post treatment) - assessment of function, complications and quality of life via postal questionnaire (or telephone interview).

Intervention (s)	Participants will be randomised to receive ORIF or CCC. **Standard care group - ORIF** Specific implant selection will not be fixed by the study but surgeons must comply with the (universally used) implant designs and concept of ankle fracture fragment reduction and fixation techniques. These specifications recognise historically proven concepts for successful internal fixation - AO Principles of Fracture Management. **Intervention group - CCC** Standardisation of the casting materials, cast design and application, and moulding technique will exist by surgeon instruction and information documentation. The method of closed fracture manipulative reduction of deformity will be left to individual surgeons and this falls within the common contemporary skills set of senior surgical trainees and consultants. All cases will conform to the NHS standard of being performed under consultant supervision and rehabilitation guidance will be the same for both treatment groups once bone healing has been confirmed as suitable to commence weight-bearing.

3. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
ICF	Informed Consent Form
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
ORIF	Open Reduction and Internal Fixation
TCC	Total Contact Casting
CCC	Close Contact Casting

4. BACKGROUND AND RATIONALE

In 2004/5 Hospital Episode Statistics recorded 338,941 Finished Consultant Episodes (FCE) for fractures that required admission or surgery. Ankle fractures account for 9% of all fractures. The literature surrounding ankle fractures shows an increasing incidence over the age of 50 years with the trend set to continue (1,2,2a). Data from the NHS (2005-6) and ONS show that 25% of these ankle fractures occur in adults over 60. The most recent quoted figures are 142 per 100,000 per year with the highest incidence of 248 per 100,000 per year occurring in women between 75 and 84 in Scotland (2) and 310 per 100,000 women per year in those over 65 years in USA (3). A three-fold increase is predicted from 2000 to 2030 as the population ages (4). This fracture is also a recognised marker of osteoporosis (2b,5) with the peak incidence in older women and young men (6). The short term disability and long-term consequences on restoring independence are considerable in the older age group. Co-morbidities are common and often multiple in the older person.
For the young adult patient the established treatment is open reduction and internal fixation (ORIF), in which the bone fragments are repositioned at surgery and held in place until healing (union) by plates and screws. This fracture occurs within the ankle joint, and in the younger patient, accuracy of fracture fragment alignment is a high priority. This reduces the long-term risk of post-traumatic arthritis resulting from eccentric loading in this weight-bearing joint. Casting methods are not generally used in young people as maintenance of fracture position is much harder, and rehabilitation is much slower. The incidence of wound problems in patients under 60 years of age is acceptably low (1-5% of cases).
The older patient however, represents a challenge to achieve that successful surgical fixation given their co-morbidities, poor bone density, frail skin and impaired wound healing. Poor bone quality (resulting from osteoporosis) directly affects the efficacy of stabilisation treatment methods for the bone fracture fragments (7). Such fractures, because of the greater fragmentation and poor bone strength, tend to be less stable after repositioning and, if used, the holding strength of fixation screws can be diminished up to 10 fold (8). This can render fixations incompetent and prevent early joint movement and weight-bearing – the accepted advantages of the surgical fixation approach in the younger patient. Other common co-morbidities in the older patient directly affect the lower limb skin and soft tissue tolerance of surgical wounds or traditional casts. Typically the older patients suffer from degrees of peripheral vascular disease, chronic venous insufficiency, late onset diabetes, and/or oedema from heart failure and skin frailty.
Current treatment in the older person still favours ORIF over non-operative treatment by fracture manipulation and the application of a standard moulded plaster of Paris cast. Both are associated with complications but the limited published research indicates higher

complication rates of fracture malunion (poor position at healing) with casting. Traditional casting methods can also create pressure sores. Wound breakdown and loss of implant fixation with ORIF occurs more frequently in older patients.

The management of ankle fractures in the elderly however remains controversial amongst orthopaedic surgeons in the developed world (9). Many surgeons make a clinical judgement alone on a) the likely tolerance of a patient's skin for surgical incisions and b) the bone quality and chance of achieving implant fixation. For patients judged as higher risk for open surgery, some surgeons may select manipulation and traditional casting, assuming less catastrophic complications but with a higher risk of malunion. A modification of the traditional casting treatment, with a better fracture stabilisation potential and lower skin damage risk, has now been identified – close contact casting (CCC). This is a modification of "total contact casting" used extensively and successfully for more than 20 years (10,11,12) in treating leg ulcers in diabetics who have the frailest of skin. Total contact cast is currently considered standard treatment for this diabetic patient group (13, 14). It works by creating an intimate, anatomic, very close fit to the lower leg shape so dissipating forces evenly over all the skin, avoiding high local contact areas, protecting and promoting skin recovery. CCC utilises the same theoretical basis to the treatment of ankle fractures and maintenance of fracture reduction. The CCC is applied once major swelling has subsided at a similar time to that when open surgery would be considered. The use of specific moulding points and sited pressure pads prevents fracture displacement whilst minimising the risk of skin damage.

Potential Benefit

Patients, particularly the more senior or those with other medical conditions, often declare a preference not to have surgery recognising the risks of anaesthesia and infection. Reduced activity demands in older life may also be a factor in their expectations of functional need. For the younger patient ORIF offers more mobility and early weight-bearing during the acute treatment phase; this is frequently not available to the older person. It is likely that for many older people, CCC may be an attractive equivalent or preferable treatment compared to open surgery.

Potential benefits to the healthcare provider of CCC treatment, identified in a feasibility study for this proposal, include no implant costs, reduced operating theatre time and a shortened length of stay. In addition there are no potential secondary operations for removal of prominent metal implants. Secondary operation rates can be as high as 32% with a cost difference as high as 4.5 (15). Pain can also be a problem for people undergoing ORIF - Brown et al (16) reported 31% of 126 patients had persisting pain over the fracture hardware, which was associated with a reduction in SF-36 and SMFA (Short Musculoskeletal Functional Assessment) scores at final follow-up (17).

Existing Research

We have been preparing for this study for 3 years, during which we have updated existing systematic reviews, identified new trials, searched trial registers and undertaken laboratory, pilot and feasibility studies to add to the knowledge base and inform study design. Despite the common occurrence of ankle fractures in older people published research is considered of poor quality (3,18). Non-consecutive case series, non-randomised and retrospective reviews dominate. Follow up is often incomplete, and there is a reliance on data abstracted from records and radiographs as opposed to the patient-important and functional outcomes. There is little published evidence to predict the late incidence of post-traumatic arthritis, but pragmatically it is of less concern in the older person.

There are advocates and published series supporting open surgery as well as traditional cast treatments. Egol et al (19) demonstrated that patients who were younger than forty were more likely to recover 90% or more of function ($p = 0.004$). Fitness for anaesthesia (ASA Class 1 or 2) was also predictive of better functional recovery ($p = 0.03$) (19). The ASA classification is the American Society of Anaesthetists performance status score. It uses a scale of 1 to 5, with 5 representing highest anaesthetic risk (20).

In the elderly, rates of postoperative complications from ankle fracture fixation surgery are high (15). Infection is reported in up to 12% and unsatisfactory results in 42%. Soft tissue complications after surgery have a negative effect on long-term functional outcome (21). This has led to recommendations by some for non-operative treatment. More recent case series studies in the elderly (22,23) support ORIF for a more predictable good outcome and acceptably low complication rates. A more comprehensive analysis (24) of a case series of 74 patients over 70 years of age concluded that poor bone precluded surgery in 12%, wound edge necrosis occurred in 9% and malunion in 5%. Vioreanu et al (25) in a retrospective unmatched case-note review series (118 patients) stressed the importance of individual evaluation. They reported surgical complications of 8.2%, including wound complications or breakdown, one ankle fusion and one below knee amputation in 72 ORIFs. This compared to a 27.2% failure to hold fracture reduction in 40 patients treated by traditional casting. There was no functional assessment but they reported a restoration of previous mobility levels being achieved by only 72% of the ORIF and 45% of people treated with a traditional cast respectively (25). The ORIF group were younger, had lower co-morbidity scores and better pre-injury and final mobility. The only prospective randomised trial (15) using a validated scoring system demonstrated that in 65 patients, significantly better scores were achieved in the non-operative group. The only other RCT compared conservative and operative treatment in patients over 55 years of age (26); of the 47 participants, 4 were excluded and 7 were lost to follow-up. A recent meta-analysis by Petrisor in 2006 (18) identified only the 2 small RCTs (reference 15 and 26 as discussed above) out of 24 potentially relevant publications. They pooled functional scores using mean effect size for

157 ORIF and 134 traditional cast participants only. They found operative fixation tended to reduce the risk of an adverse outcome (OR=0.68 CI: 0.30-1.2, p=0.08) but the 2 studies revealed divergent results in patient function - one favouring ORIF and the other non-operative treatment. Given the limitations of current trials they concluded it was difficult to give recommendations for practice.

A recent comprehensive review (9) also recognised this treatment controversy in the orthopaedic surgical community for the geriatric patient and quoted an increasing ankle fracture incidence with elderly obesity, poly-pharmacy and the falls risk as key factors. They concluded that early ORIF studies cited high complication rates but more recent evidence appeared to support surgery. They found only 4 small comparative studies between 1983 and 2007 with participant numbers ranging from 47 to 126. A second large review of 33,704 American Medicare patients over 65 years, showed the incidence of complication rates in both operative and non-operative treatments to be low - less than or equal to 2% (27). Bhandari (3) in a prospective cost analysis of operative treatment (all ages) recorded a significant health gain (mean Health Utilities Index of 0.78 at 1 year) at reasonable cost ($2143). Delayed healing, infection or dehiscence of surgical wound may generate the greatest treatment costs and disability.

To add to the knowledge base and inform trial design, a feasibility study (28) was undertaken by the chief investigator in Oxford with 50 participants using concealed randomisation; that has confirmed the viability of the study design and outcome measures proposed. It has also provided data to inform the estimates of effect and sample size, along with recruitment rates. Parallel vascular laboratory have confirmed the potential for improved skin viability outcomes with the CCC. There is a timely need for a properly constructed randomised controlled trial comparing optimal contemporary treatments, both for patient-important outcomes and cost effectiveness. This research question was a product of a research priority setting exercise undertaken in 2007 with the 150 orthopaedic trauma surgeon members of AOUK (UK Association for Osteosynthesis) to identify research areas of importance for surgical fracture treatment. The CCC represents the optimal current cast method (the proposed intervention); ORIF is the active comparator and represents current common practice.

4.1 Primary Objective

To determine if the application of the “close contact casting technique (CCC)” for displaced ankle fractures in older adults results in an equivalent outcome compared to the standard care of open surgical internal fixation (ORIF) in terms of function, complications, quality of life and patient satisfaction with treatment.

4.2 Secondary Objectives

An economic evaluation will run in parallel to the study and will consider the costs of the two treatments to (i) the NHS, and (ii) the broader societal perspective including to the individual and their family. The study will be recruiting older people in an emergency situation.
Potential complications, readmissions, revision surgery rates and mortality will be monitored carefully and considered in the overall appraisal of clinical and cost effectiveness.
Ankle fracture healing takes 6-8 weeks and recovery is achieved to a steady state by 6 months; this defines the study duration and time points for data collection in this study.

5. STUDY DESIGN

5.1 Summary of Study Design

A pragmatic multi-centre randomised controlled trial with parallel prospective economic evaluation. Participants will be randomised to receive ORIF or CCC after emergency admission for surgery for displaced unstable ankle fractures in the Trauma and Orthopaedic Surgery Departments of a minimum of 20 NHS acute hospitals. A 6 month review will be undertaken to monitor changes in mobility, function, health related quality of life, complication rates, and resource use associated with each of the interventions. That review will be conducted face to face by an assessor blinded to the intervention.

Screening	Mental state – The Mini-Mental State Exam (MMSE)
Measures at Baseline (inpatient - 60 minutes)	Olerud & Molander ankle score Quality of life – EQ-5D (utilities measure) and SF-12 General health Social circumstances
Measure in theatre (inpatient - 10 minutes) implants	Radiological fracture and joint position measurement Time in and out of theatre, experience of operating surgeon, used, type of anaesthetic
Measures at 6 weeks (outpatient - 30 minutes	Olerud & Molander ankle score Quality of life – EQ-5D (utilities measure) and SF-12 Patient satisfaction measure Ankle range of movement Radiological fracture and joint position measurement Health economics assessment Semi-structured interview discussed and appointment Arranged (selected sites only)
6 -10 weeks (outpatient - 1 hour)	Semi-structured interview exploring patient experience of Treatment and study involvement (selected sites only)
Measures at 6 months (outpatient - 30 minutes)	Olerud & Molander Ankle Score Timed 'Get up and Go' test Quality of life – EQ-5D (utilities measure) and SF-12 Patient satisfaction measure

	Ankle range of movement Radiological fracture and joint position measurement Health economics assessment
Extended follow up (postal/telephone)	Measures at least 2 years post treatment To assess quality of life, complications and ankle function/mobility. Subject to funding.

5.2 Primary and Secondary Outcome Measures

Primary outcome measure:

A functional outcome based on the Olerud & Molander Ankle Score (29)

Secondary outcome measures will include:

a) Soft tissue complications (30)

b) Timed 'Get up and Go' test (31)

c) Ankle range of movement: goniometer measurement of dorsiflexion, plantarflexion, (component of the Iowa ankle score) (32), inversion and eversion

d) Radiological measurements of fracture and ankle joint congruence (33)

e) Quality of life – EQ-5D (utilities measure) and SF-12 (34, 35)

f) Patient satisfaction measure - tailored questionnaire (36)

g) Qualitative assessment by semi-structured interview of a 20 participant sample from each treatment group (selected sites only)

h) Cost-effectiveness will be measured by an economic analysis conducted along side the study and will include modelling to extrapolate beyond study data to give cost per QALY estimates. The analysis will incorporate the elements of:

- Duration of inpatient hospital stay
- Theatre time/implant costs
- Fracture Clinic visits
- Additional treatment costs
- Social dependency/support change

Collected at 6 weeks and 6 months

5.3 Study Participants

5.3.1 Overall Description of Study Participants

Men or women over 60 years with displaced unstable fracture of the ankle and are suitable for anaesthesia for both ORIF and CCC

5.3.2 Inclusion Criteria

- Men or women aged over 60 years
- Isolated displaced unstable ankle fracture
- Ambulatory prior to the injury - in any capacity
- Capable of giving informed consent
- Capable of adhering to post-operative instructions
- Resident within the catchment area of a recruiting hospital
- Can attend for 6-month follow up

5.3.3 Exclusion Criteria

- Established critical limb ischaemia
- Insulin dependent diabetes mellitus
- Active leg ulceration
- Open fractures
- Serious concomitant disease - metastatic disease or terminal illness
- Clinically substantial degenerative or inflammatory arthritis (in the ankle)
- Unfit for anaesthetic
- Unable to give informed consent - cognitive impairment demonstrated by Mini-Mental State Exam (MMSE) of under 16/30 (37)
- Patient unwilling to give informed consent

5.4 Study Procedures

Participant approach and recruitment

In all participating centres, new admissions will be reviewed each day by the surgical team. In line with normal practice in the NHS this will include a review of X-rays by the surgeon (and usually a radiologist). A part-time research nurse will be recruited to each site. Geographical proximity of some of the sites means that a full-time nurse may cover several sites. Where possible for cost efficiency we will contribute to an already established research nurse resource. The research nurses will ensure that surgeons consider all potentially eligible admissions, and will refine systems to best fit with local protocols. The treating surgical team will undertake the initial approach to participants, explaining that a study of ankle fracture treatments is being conducted. It will be important at this stage that clinicians do not inadvertently influence potential participants by describing only one of the possible options. If the participant is willing, a member of the research team will explain the study in more detail and check eligibility criteria. Participant cognitive function will be assessed to ensure it is sufficient to provide informed consent, and an explanation of the study options

and procedures provided. Potential participants will be given as long a time as possible to consider participation; traditionally most treatment is delayed a few days to allow injury swelling to settle. This is a prerequisite for both interventions.

Randomisation

The unit of randomisation will be the individual. We will use a 24-hour telephone randomisation service to ensure allocation concealment. Randomisation will be stratified by recruiting centre and . fracture pattern, using trans-syndesmotic and supra-syndesmotic categories as required. A few people will fracture the contra-lateral ankle during follow up. If this is the case, they will, if clinically indicated, receive the treatment they were originally assigned, in the second ankle. The original injury will be the index.

Baseline Assessments

Baseline data will be collected by the research nurses from all participants and will include age, sex, and general medical history. Information on the patients chronic disease burden will be collected. None of the participants will be ambulatory at the baseline phase, but we will collect information about pre-injury mobility status using the Olerud & Molander ankle score (29) and health related quality of life (using the EQ-5D and SF-12). Although not ideal, recall is the only method that we will have of assessing pre-fracture abilities. As the recall period is relatively short, we do not anticipate problems. The type of residence (own home, warden accommodation, residential home, nursing home, rehabilitation, acute hospital, community hospital or temporary residence) in the month prior to admission will be recorded, as will the level of support provided and whether the participants lived alone prior to the injury. The EQ-5D will also be used to collect with injury data at baseline.

Planned Interventions

Participants will be randomised to receive ORIF or CCC. Specific implant selection will not be fixed by the study but surgeons must comply with the (universally used) implant designs and concept of ankle fracture fragment reduction and fixation techniques. These specifications recognise historically proven concepts for successful internal fixation - AO Principles of Fracture Management (38). For the CCC group there will be standardisation of the casting materials, cast design and application, and moulding technique. This will be by surgeon instruction and information documentation - (Appendix 1). The method of closed fracture manipulative reduction of deformity will be left to individual surgeons and this falls within the common contemporary skills set of senior surgical trainees and consultants. All cases will conform to the NHS standard of being performed under consultant supervision.

Blinding, contamination and bias

Participants will attend for a study assessment, concurrent with standard clinical reviews, at follow-up clinics at 6 weeks and 6 months. At these appointments, the patient will undergo a routine clinical review, including an x-ray and clinical assessment. A copy of the x-ray or original digital image will be sent to the central trial office (Appendix 2), The radiographs will be reviewed centrally by a trained independent assessor. Measurements will then be verified by two independent surgeons. Any disagreement will be resolved by a radiologist.
At 6 months a health professional, who is blind to treatment assignment, will complete the functional assessments, mobility test and ensure completion of the study questionnaires. We are confident that with usual safeguards it will be possible to blind the assessors to assignment. Presence or not of the surgical incision will be obscured by an opaque bandage applied prior to the assessment (Appendix 3). We will undertake a post-hoc analysis of the success of the blinding strategy. All participants will be assessed by an unblinded orthopaedic surgeon to deal with any ongoing symptoms such as pain or symptoms related to plating (eg: prominence of implants). It will not be possible to blind the treating surgeon or x-ray assessors during follow-up to the intervention. The implants, or their absence, will be apparent on the x-rays as will the soft tissue scars on examination. The trial management group and steering committee will remain blinded until the final analysis is complete.
Within this trial there is the potential for clinical imperative to change the intervention. Such circumstances include:

1) After randomisation at the point of intervention with anaesthesia commenced, the temporary cast is removed. The ankle skin condition may have deteriorated such that the surgeon considers one or all necessary surgical incisions to be unsafe. If randomised to ORIF, an alternative treatment (*) would be given.
2) After randomisation at the point of intervention with anaesthesia commenced, a fracture may prove irreducible by closed manipulation. The surgeon would necessarily proceed to open surgical reduction. If that is required plate internal fixation would be undertaken.
3) If there is an unacceptable loss of position by either treatment method prior to fracture healing. The surgeon will adopt the treatment approach (*) best judged to achieve a favourable outcome.
4) Very rarely a combination of bone and skin fragility and gross joint instability will exclude either intervention. The surgeon will apply a temporising external fixator and definitive treatment (*) will be at the surgeon's discretion.

(*) alternative treatments include i) traditional plaster cast, ii) external fixation iii) ORIF. CCC will be excluded as an option outside the group randomised to CCC.

Surgical training

Surgeons will follow standard AO fracture reduction and fixation techniques and manufacturers' recommendations for implant insertion for ORIF. The techniques, designated by the study, are common UK surgical practice and lie within the expertise of UK trained and senior training orthopaedic surgeons. The study will ensure that all operating surgeons will have completed training that is consistent with the requirements of contemporary practice in the NHS before being permitted to utilise the surgical or casting techniques. This will include using educational materials and reference to surgical technique manuals.

Learning and expertise effects

This is a pragmatic study. We will monitor and analyse data to establish the extent, if any, of learning or expertise effects. It is common practice that surgeons have particular expertise in selected techniques, and for surgical teams to organise their workloads so that expertise is utilised to best effect. This study will not interfere with this dynamic. It is therefore not easy to anticipate the direction of expertise and learning effects. For each surgeon participating in the study, we will collect the following information: historical experience and preferences for ORIF and casting, grade of surgeon, time since qualification as a surgeon, time since first operation on the study. We will analyse the data for evidence of learning and expertise effects. This will then guide recommendations on implementation and training if the technology proves effective.

Standardisation of other treatments

We will record time to treatment (in hours from the time of admission) and type of anaesthesia (regional, general or both). There is no reason to believe that these factors will not be evened out by randomisation. The pre-operative preparation of patients will be standardized in both study arms. The post-operative management plan will be left to the individual surgeon but in few patients will weight-bearing earlier than 4-6 weeks be recommended. Rehabilitation will focus on early restoration of independent mobility. We recognise that for some of the frailer patients this will not be achieved to a level that will restore independent living in the healing phase of 6-8 weeks. We will give guidance on acceptability of position and minor displacement but as a pragmatic trial this will ultimately be a local clinical decision.

Each hospital's Infection Control Committee will set the pre-operative antibiotics prophylaxis protocol for the type of implant-insertion procedure for the ORIF group; this will reflect the incidence and strains of potentially contaminating organism in their hospital. In reality there is likely to be consistency between hospitals. No antibiotics will be routinely administered to the CCC patients in theatre. Thromboprophylaxis will reflect local hospital policy and be identical for both groups. Unfractionated heparin, low molecular weight heparin, warfarin or

anti-platelet agents with or without mechanical compression or pump devices are normal practice.

Follow up procedures

Follow-up will be maximised by maintaining contact with trial patients intermittently through the trial by letter, email and/or telephone. Accurate contact details of patients will be obtained at the first hospital admission. Prior permission will be obtained to use these contacts to track the patients' subsequent progress. In addition we will use The NHS Information Centre for Health and Social Care Medical Research Information Service or General Practitioner to track patients who move home. Follow-up trial assessments will coincide with the normal trauma clinic follow-up visits as part of their care. Patients unable to attend will be contacted by telephone, or visited at home. Data will be entered using a validated document scanning system - Teleform^{M} (39,40) at the trial co-ordinating office to avoid manual data entry error and identify early incomplete fields to optimise complete and accurate data.

During the extended follow up period (at least 2 years post treatment), participants will be asked to complete a postal questionnaire (or data may be collected by telephone interview if participants prefer).

5.4.1 Informed Consent

Research nurses will be trained to take consent for study entry prior to any study related procedures being undertaken. They will explain the study in detail, check eligibility criteria and assess cognitive function to ensure ability to provide informed consent. This is likely to occur within an inpatient setting but for a minority may be in an outpatient department. Potential participants will be given as long a time as possible to consider participation as most treatment is delayed for several days to allow injury swelling to settle. This is a prerequisite for both interventions.

The research nurse will also be responsible for ensuring that the surgical team are aware of the recruitment, treatment assignment, and that theatres are appropriately prepared for the procedures.

5.4.2 Study Assessments

Screening assessments

These are primarily radiological in order to classify the fracture, but will also include the clinical evaluation undertaken by the admitting surgeon and his/her team. They will then inform the study team of those potential participants happy to be approached.

Baseline assessments - 30 minutes

To be undertaken by one of the research team following consent and prior to randomisation. They consist of short, multiple choice questionnaires covering pre-injury function, general health and social circumstances. There is also a cognitive function assessment to establish

ability to provide informed consent. The assessments take 30 minutes to complete in total.

- Olerud & Molander Ankle Score - a patient reported functional outcome measure. Questions covering areas of physical ability
- EQ-5D (prior to injury and with injury), and SF-12: Quality of life / utilities measure. Questions covering aspects of well-being and a visual analogue scale to describe general health state
- General health - Questions relating to medical history, smoking and drinking usage, allergies and medication
- Mini-Mental State Examination - MMSE - Questions to assess cognitive function
- Social circumstances - Questions to ascertain place of residence and care requirements

Theatre assessments - 10 minutes

To be undertaken by member of theatre team under supervision of research surgeon

- Time in and out of theatre, experience of operating surgeon, implants used, type of anaesthetic, complications
- Radiological measurements of fracture and ankle joint congruence (acceptability of position by treating clinicians but x-rays to be sent to the Oxford Trials Unit for detailed measurement)

6 weeks - 30 minutes

To be undertaken by member of research team

- Olerud & Molander Ankle Score - a patient reported functional outcome measure. Questions covering areas of physical ability
- EQ-5D and SF-12: Quality of life / utilities measure. Questions covering aspects of well-being and a visual analogue scale to describe general health state
- Ankle range of movement - goniometer measurement of dorsiflexion, plantarflexion, inversion and eversion
- Radiological measurements of fracture and ankle joint congruence (acceptability of position by treating clinicians but x-rays to be sent to the Oxford Trials Unit for detailed measurement)
- Patient satisfaction measure - tailored questionnaire
- Cost-effectiveness will be measured by an economic analysis conducted along side the study and will include modelling to extrapolate beyond study data to give cost per QALY estimates. The analysis will incorporate the elements of:
  - Duration of inpatient hospital stay
  - Theatre time/implant costs
  - Fracture clinic visits
  - Additional treatment costs

- Social dependency / support change at 6 months

Data will be collected at 6 weeks and 6 months.

- Discussion of sub-study and arrangement of interview - A qualitative assessment of 20 participants from each treatment group at 2 participating sites

6-10 weeks - 60 minutes

To be undertaken by qualitative researcher (selected sites only)

- Semi-structured interview, conversational in style

6 months - 30 minutes

To be undertaken by member of research team (blind to intervention)

- Olerud & Molander Ankle Score - a patient reported functional outcome measure. Questions covering areas of physical ability
- EQ-5D and SF-12: Quality of life / utilities measure. Questions covering aspects of well-being and a visual analogue scale to describe general health state
- Ankle range of movement component – goniometer measurement of dorsiflexion, plantarflexion, inversion and eversion
- Radiological measurements of fracture and ankle joint congruence (acceptability of position by treating clinicians but x-rays to be sent to the Oxford Trials Unit for detailed measurement)
- Patient satisfaction measure - tailored questionnaire
- Timed 'Get up and Go' test - to assess mobility
- Health economics/cost-effectiveness data (as at 6 weeks)

Extended follow up period

- At least 2 years post treatment
- Postal questionnaire/telephone interview to assess quality of life, complications and ankle function/mobility

5.5 Definition of End of Study

The end of main study is the date of the last 6 month outpatient appointment of the last participant.

6. INTERVENTIONS

Participants will be randomised to receive ORIF or CCC.

6.1 Standard Care:

Open surgical Reduction and Internal Fixation - ORIF
Specific implant selection will not be fixed by the trial but surgeons must comply with the (universally used) implant designs and concept of ankle fracture fragment reduction and fixation techniques. These specifications recognise historically proven concepts for successful internal fixation - AO Principles of Fracture Management.

6.2 Intervention:

Manipulation under anaesthetic and application of close contact cast - CCC
Standardisation of the casting materials, cast design and application, and moulding technique will exist by surgeon instruction and information documentation (Appendix 1). The method of closed fracture manipulative reduction of deformity will be left to individual surgeons and this falls within the common contemporary skills set of senior surgical trainees and consultants.
All cases will conform to the NHS standard of being performed under consultant supervision and rehabilitation guidance will be the same for both treatment groups once bone healing has been confirmed as suitable to commence weight-bearing.

7. SAFETY

Adverse events resulting from medical co-morbidities or anaesthesia (part of normal care) will only be recorded as adverse events (AEs) and not reported as SAEs. Expected complications including wound breakdown, loss of fracture position, etc will also be recorded as adverse events only.

7.1 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death within 30 days of surgery
- Results in death related directly to the surgical intervention at any time
- Life or limb threatening complication

- NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Re-hospitalisation
- NOTE: Hospital stay for removal of syndesmosis screws will be reported as an AE only as it is an expected part of normal care

7.2 Reporting Procedures for Serious Adverse Events

Serious adverse events (SAEs) must be reported to the Chief Investigator in the first instance. A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs will be submitted by the Chief Investigator within 15 days of his becoming aware of the event, using the NRES report of serious adverse event form.

8. STATISTICS AND ANALYSIS

8.1 Number of Participants

Given the paucity of data in the published literature the feasibility pilot data have been used as a primary source to inform estimates of variance and treatment effects measured using the Olerud & Molander score, and a range of secondary outcomes. We have tested the sensitivity of these estimates against data available in the published literature.

Although the original sample size estimate was based on a difference in proportions this was modified by the DMEC as data from the pilot study confirmed data to be normally distributed and that analysis based on a continuous score would be more efficient and meaningful. Parameters for the sample size were informed by data from the pilot study, known only to the study statisticians and DMEC. We utilised one-sided testing ($p = 0.05$) since we are not trying to prove that the new treatment is better than the standard, and gain considerable statistical efficiency (50). Power was set at 80% according to Food and Drug Administration (FDA) recommendations for bioequivalence studies (51).

Based on the mean difference observed between the groups of 2.6 points in the first 71 participants from the pilot study, pooled standard deviation of 16.2, an equivalence margin of +/- 6 points on the Olerud & Molander Ankle Score, yields a final sample size of 560 in total (50). We inflated for loss to follow up of near 10% yielding a total sample size of 620. Published estimates to inform the selection of equivalence margins using the Olerud & Molander Score was non-existent. Using the pilot data to calculate standardised effects sizes, the equivalence margin includes small differences (<0.37) but excludes moderate or large treatment differences. This was consistent with clinical opinion supporting a 6 point margin excluding clinically important differences in this condition gathered in an informal survey of orthopaedic surgeons, and published data on the minimally clinically important differences for similar scores (Foot and Ankle Score, and visual analogue pain scores in acute injury) that report minimally clinically important differences greater than 10 points on a 100 point scale.

8.2 Analysis of Endpoints

In equivalence testing a maximum clinical difference (Δ_T) is pre-specified at a level within which the two treatments can be considered not to differ in any clinically meaningful way. Therefore, the relevant null hypothesis is that a difference of greater than Δ_T exists in either direction, H0: $\Delta \leq -\Delta_T$ or $\Delta \geq \Delta_T$, and the trial is targeted at disproving this in favour of the alternative that no clinical difference exists, HA: $-\Delta_T < \Delta < \Delta_T$. FDA regulations recommend both a treatment received (per-protocol) and intention to treat analysis, aiming to demonstrate equivalence (51). Use of an ITT approach as in a superiority trial sometimes increases the chance of falsely claiming equivalence (52, 53). Initially, a per-protocol analysis will be undertaken where only the patients who received their allocated treatment will be analysed and those patients who did not, will be excluded from the analysis. Following this an intention to treat analysis will be carried out where all randomised patients will be analysed according to the treatment they were randomised to.

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

- The confidence interval for the difference between the two treatments lies entirely within the equivalence range, $-\Delta_T$ to Δ_T, so that equivalence may be concluded with only a small probability of error.
- The confidence interval covers at least some points that lie outside the equivalence range, so that differences of potential clinical importance remain a real possibility and equivalence cannot safely be concluded.

- The confidence interval is wholly outside the equivalence range (though this is likely to be rare).

As well as assessing if equivalence is demonstrated in either case this will also form part of an additional sensitivity analysis to assess the range of potential biases that could have resulted from loss to follow-up, protocol deviations, withdrawal (and mortality). Numerical and graphical summaries of all the 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 equivalence will also be presented. Our main analytical methods will be generalised linear models, and all analyses will adjust for important baseline co-variants to maximise precision.

The Olerud & Molander Ankle Score at 6 months is the primary outcome in this study and will be compared between treatment groups as the dependent variable in a linear regression model for the primary analysis. The treatment difference will be based on the estimates of the adjusted means and 95% confidence intervals. The Olerud & Molander Ankle score will also be presented as an ordinal outcome in a secondary analysis using ordered logistic regression or non-proportional odds models, depending on the validity of the proportional odds assumption, will be carried out. Secondary outcome measures will be similarly analysed with logistic regression models being used for categorical data and linear regression models for continuous data. Time to event data (e.g. time to discharge) will be analysed using a log-rank test. Any patients who have not experienced an event at the time point of interest or withdrew will be censored. The proportion in each treatment group experiencing an event over time will be illustrated using a Kaplan-Meier curve. The p-value and a hazard ratio with its 95% CI from a Cox proportional hazards model will also be presented. The proportional hazards assumption across treatment arms will be checked graphically using a log-cumulative hazard plot. A data analysis plan will be agreed with the Independent Data Monitoring Committee.

Economic analyses

The costs of the treatment will include implants, cast material, radiographs, surgical operating time hospital and rehabilitation length of admission, and post-operative care. Resource use will be collected during the follow up period and will consider major costs falling on the health service and personal social services (corresponding to the NICE reference case). We will also look at the broader societal perspective to include social services costs and costs falling on individual patients/carers. These will be valued in monetary terms by applying unit costs from standard sources such as the NHS Reference

costs and the PSSRU Costs of Health and Social Care. The outcome measure will be the Quality Adjusted Life Year (QALY), based on the EQ-5D instrument with utility weights taken from the UK General Population tariff (41). All costs and outcomes will be discounted at 3.5% per annum as per the NICE reference case (42).

Two timeframes will be considered for the economic evaluation - a six-month timeframe to correspond to the observed data from the clinical trial and a lifetime analysis which will be based on projection of the clinical trial data using decision-analytic modelling techniques (43). Cost-effectiveness will be presented from both the NHS/Personal Social Services perspective and the broader societal perspective.

Uncertainty for the six-month analysis corresponding to the period of the trial will be handled through non-parametric bootstrapping. Uncertainty for the additional parameters introduced as part of the modelling projection will be handled using probabilistic sensitivity analysis based on Monte Carlo simulation. Sensitivity of the analysis to individual parameter uncertainty as well as overall decision uncertainty will be assessed and presented (44).

A separate sensitivity analysis will explore the potential importance of including productivity (indirect) costs of patients / carers alongside direct costs in the societal perspective analysis. This analysis will be based on estimates of days lost from work in combination with alternative methods for valuing a day's productivity.

Mobility – using the Timed 'Get up and Go' test

Mobility has been selected as the primary measure at 6 months, because it is a highly sensitive measure, is important to patients and is important for independent living. The Timed 'Get up and Go' test is a simple test specifically designed for frail older people – it records time taken to get up from a chair, walk a short distance and sit down again. Performance tests are a recognised standard for measuring mobility and associations with important end points including risk of falling, functional decline and institutionalisation (45).

Pain

No separate pain linear analogue score will be used. Both the Olerud & Molander Score and the EQ-5D include pain and will be analysed by component.

Health related quality of life – using the EQ-5D

Recent systematic review and consensus meetings have concluded that the EQ-5D is sensitive to the types of change we will observe in this frail population. It is also simple to complete (46).

Complications and revision surgery (and mortality)

For both groups X-rays will be taken post-operatively, at 6 weeks and 6 months, Patients in the CCC group will require monitoring x-rays on average on further 2 occasions to check maintenance of fracture position and after any interval cast changes (if required). Fracture healing, union, fracture and joint position will be assessed on standard anteroposterior (ankle mortise view) and lateral radiographs using standard measures of joint congruence, fracture angulation and fibular shortening. Dislocation or subluxation will be evident. The standard measurements will be:

Talocrural angle	≥ 5 degrees
Medial clear space	≤ 4mm
Medial malleolar displacement	≤ 2mm
Lateral malleolar displacement	≤ 2mm
Tibiofibular clear space	< 5mm
Tibiofibular overlap	≥10mm
Talar tilt	≤ 2mm
Talar subluxation	Yes / no
Fibular shortening	Yes / no
Fracture union	Yes / no

Changes in care status or domicile will also be captured. The hospital Patient Administration System will be interrogated to capture hospital re-admissions for additional treatment such as revision surgery. It will also identify adverse events requiring mandatory monitoring and reporting. Data sources will be the participant, relative or hospital records. Other fractures sustained or major illness resulting in disability in the study period will also be recorded. Mortality will be reported at 30-days and 180-days. No difference between the groups is anticipated.

Qualitative Study

In order to explore patient experience of their treatment and recovery a purposive sample of 40 patients will be interviewed using a semi structured interview schedule between 6-10 weeks post treatment. The sample will cover patients from: both treatment options; two study sites; a range of age, sex, and accommodation. Participants will be fully informed and provide written consent. The interview will be conversational in style to allow patients to identify their experiences and the issues that concern them. The research question will be; what are the experiences of patients with an unstable ankle fracture? The key interview questions will cover what it is like to have an unstable ankle fracture; their experiences of treatment, what it is like living with a cast and their experience of treatment with surgery.

This will be followed by prompts such as: tell me more about that; how did that affect you; how did you feel about that; how did you manage. To ascertain the impact of the trial on the participants they will also be asked, what is it like to take part in a trial. The interview will be taped and transcribed verbatim. Analysis will be line by line, identifying codes, building categories and themes, drawing on the work of Miles and Huberman (47). NVivo7 a software package for qualitative data will be used to help with data management. The intention is to understand how patients make sense of their treatment and recovery and whether there are any differences in experience between the two treatments.

9. ETHICS

9.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so (48).

9.2 Other Ethical Considerations

Ethics and R&D Committee approval

Oxfordshire REC A (Type 3) has given approval for this multi domain study with data from the pilot being analysed in the main study. Site specific information submissions to the local RECs and Research and Development (R&D) departments for each participating hospital will also be obtained. We will comply with the Medical Research Council Good Clinical Practice guidelines (49), and the trial will run under the Standard Operating Procedures (SOPs) of Warwick University Clinical Trials Unit (CTU) and Oxford University. A Trial Steering Committee (TSC) will be formed with an independent chair, 2 other independent members and the principal investigators. An independent DMEC will be chaired by a statistician. Our nominated expert for the DMEC is Professor David Marsh (Professor of Orthopaedic Surgery, Royal National Orthopaedic Hospital, UCL, London). Twice yearly meeting are planned with an option to increase if specific concerns arise. All trial implants are approved by the Medical Devices Agency.

Anticipated benefits and justified risks for trial participants and society

Limb fracture interventions, including open and closed procedures, have potential risks that include wound infection, loss of fracture position, deep vein thrombosis, neurovascular injury and in the elderly, peri-operative death. All patients eligible for the study require anaesthesia and face those risks in any event. Contemporary practice and advice is based on an extrapolation of established concepts for treating fractures in the good quality bone of young patients. This is despite the presence of local and systemic aging and disease effects in older people.

Informing potential trial participants of possible benefits and known risks

The participants are acutely injured and require a reparative intervention. Potential participants will receive full and unhurried explanations of the study. Research nurses will also be available to receive questions on the study from patient relatives which was a common event in the feasibility phase. For the patient the decision is primarily between two types of procedure, both under anaesthesia. The surgical/non-operative intervention randomisation, although appropriately presented in equipoise, can be expected to generate some patients who will decline entry to the trial. There are no risks to participants over and above those already detailed in this document relating to the complications specific to the two interventions and a full explanation is given in the trial Patient Information Leaflet.

Obtaining informed consent

Mental capacity sufficient to comprehend the study objectives and design is inherent in the inclusion and exclusion criteria.

10. DATA HANDLING AND RECORD KEEPING

All study data will be entered on to a database using a validated document scanning system - Teleform^{M} to avoid manual data entry error and identify early incomplete fields to optimise complete and accurate data collection. All data will be processed according to the Data Protection Act, 1998 (48). It will be anonymised at the source hospital and held centrally on a secure database in Oxford. Data files transferred for statistical analysis will be encrypted. Trial documentation will be retained for 5 years after completion of the data collection. The participants will be identified by a study specific participants number and/or code - the name and any other identifying detail will NOT be included in any study data electronic file. A Data Co-ordinator will be appointed in Oxford. Data will be encrypted and transferred to a secure database at Warwick Clinical Trials Unit for statistical analyses as appropriate.

11. FINANCING AND INSURANCE

11.1 Finance

Participating sites

- Research nurse - Agenda for Change: Band 6 - 0.25 whole time equivalent (WTE). This will cover the recruiting period and 6 months follow up period for each site. Where possible, two sites may be covered by a single research nurse.
- Provision of stopwatch and goniometer for functional assessments
- Provision of computer if required

11.2 Insurance

Negligent Harm

The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided.

Non-Negligent Harm

The University has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor.

12. Publication Policy Statement

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. The authors will acknowledge that the study was carried out with support from the National Institute for Health Research: Health Technology Assessment programme.

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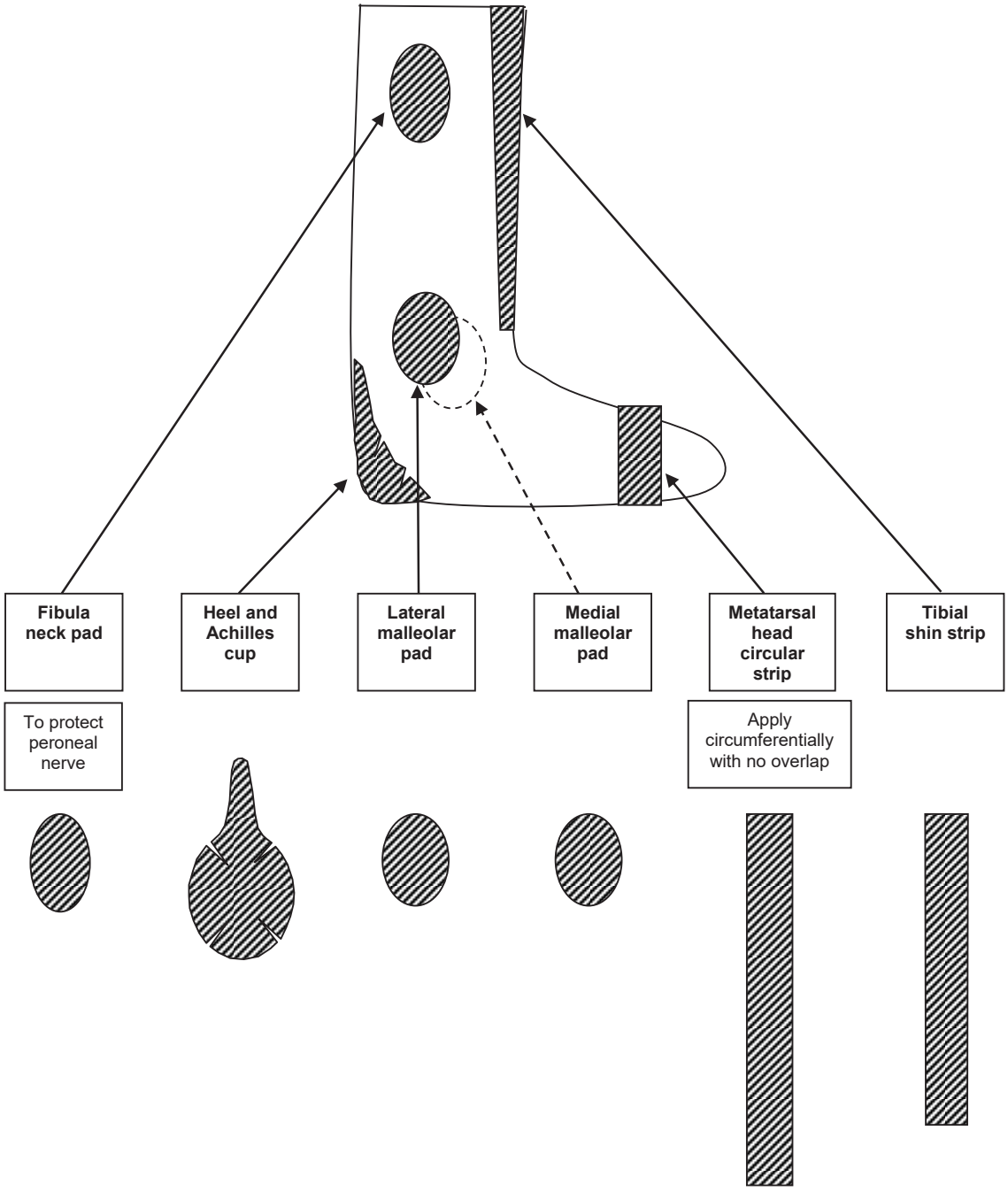
14. APPENDICES

14.1 Appendix 1: CLOSE CONTACT CAST APPLICATION



14.2 APPENDIX 2: RADIOLOGY DATA TRANSFER

- X-rays required at the following time points:
  Diagnostic - AP (mortice) and lateral at presentation
  Theatre - AP (mortice) and lateral (fluoroscopy)
  6 weeks - AP (mortice) and lateral out of cast
  6 months - AP (mortice) and lateral
- Liaise with the radiology department to have hard copy x-rays or digital images transferred to CD.
- Images should be encrypted before sending to the trial office (if encryption is not available contact the trial office)

Researcher to arrange transfer all x-ray images to CD at the end of the 6 month follow up period and send to Oxford Trials Unit by recorded delivery

Address: AIM Trial Manager
Kadoorie Centre, Level 3
Radcliffe Hospital Hospital
Oxford
OX3 9DU

14.3 APPENDIX 3: BLINDED ASSESSMENTS

These can be undertaken by one of the research team who can then identify a second health care professional to complete the blinded assessments required at 6 months. It will be the researcher's responsibility to:

- Apply an occlusive dressing to both lateral and medial side of the affected ankle
- Ensure that the blinded assessor is not inadvertently given treatment information prior to performing assessments
- Request that patient keeps treatment unknown

Baseline

All baseline assessments can be undertaken by unblinded assessor

Theatre

Undertaken by unblinded assessor

6 weeks

Undertaken by unblinded assessor

6 months

- EQ-5D and SF12 questionnaires - complete for that day. If unable to read for themselves, do not deviate from wording or discuss suitable answer - suggest they pick the closest of options and reassure that there are no right or wrong answers.
- Olerud & Molander Ankle Score - complete for that day.
- Health economics - will need completing with patient who may not have all information on the day. Physiotherapy departments / GP surgeries etc may need to be contacted directly for number of attendances.
- Timed 'Get up and Go' - place 'British Standard Height' chair with arms at one end of corridor. Ask to stand and walk safely as fast as possible (with frame / stick if still using one). Mark a point on the floor 8.6 metres from the chair and ask them to turn at that point without touching anything such as the wall. Return to chair and sit as quickly as possible. Time from moment they start to stand until moment they are sitting again.
- Range of movement measurements: see below

Assessing Range of Movement

Angle of dorsiflexion	(normal range 0-20˚)
Angle of plantar flexion	(normal range 0-50˚)
Angle of inversion	(normal range 0-35˚)
Angle of eversion	(normal range 0-15˚)

Dorsiflexion and Plantarflexion

Starting position - Patient lying at 45 degrees with pillow under lower legs to lift the heels off the surface. The foot is in the neutral position. If it is not possible for the patient to get into the starting position then the measurements could be taken in sitting, as long as the knee remains more than 20 degrees flexed and the heel is not directly resting on a support.

Goniometer axis -The axis is placed approx 1.5cms inferior to the lateral malleolus.

Stationary arm - Parallel to the longitudinal axis of the fibula, lining up with the fibula head

Moveable arm - Parallel to the longitudinal axis of the 5th metatarsal

Instructions: Ask patient to pull foot towards them (dorsiflexion), then to point away (plantarflexion). Measure angle between stationary and movable arms in degrees.

Inversion and Eversion

Starting position - Patient lying at 45 degrees with pillow under lower legs to lift the heels off the surface. The foot is in the neutral position. Stand at the patient's feet facing their head.

Goniometer axis - The axis is placed where the longitudinal axis of tibial shaft and second ray converge.

Stationary arm - Along the longitudinal axis of the tibial shaft

Moveable arm - Along the longitudinal axis of the second ray

Instructions: Looking at the angle between the tibial shaft and the second ray, ask the patient to turn their feet inwards (inversion) and measure the angle between stationary and movable arms in degrees.

Repeat asking the patient to turn their feet outwards (eversion).

(Researcher to arrange transfer all x-ray images to CD at the end of the 6 month follow up period and send to Oxford Trials Unit by recorded delivery)

14.4 APPENDIX 4: UNBLINDED ASSESSMENTS

Baseline

All baseline assessments can be undertaken by unblinded assessor

- EQ-5D and SF12 questionnaires - to be completed as how they were prior to their injury and often require prompts to remember. If unable to read for themselves, do not deviate from wording or discuss suitable answer - suggest they pick the closest of options and reassure that there are no right or wrong answers. One EQ-5D also relates to 'today, with injury'.
- Alcohol units: Average glass of wine = 2 units
  Average bottle of wine = 9 units
  Pint mild beer / lager = 2 units
  Pint strong beer / lager = 3 units
  Single spirit = 1 unit
- Smoking - Ask for average per day at the time they smoked most heavily
- Olerud & Molander Ankle Score - Also complete as how they were prior to injury. This makes Question 6 appear inappropriate so complete as 'same as before injury'

Theatre

All data collection

6 weeks

- EQ-5D and SF12 questionnaires - complete for that day. If unable to read for themselves, do not deviate from wording or discuss suitable answer - suggest they pick the closest of options and reassure that there are no right or wrong answers.
- Olerud & Molander Ankle Score - Question 1 can be confusing for some participants. Consider amount of pain and choose appropriate score rather than walking surface as most will have been non-weight bearing to that point.
- Range of movement measurements (details above in 'Appendix 3')..
- Health economics - will need completing with patient who may not have all information on the day. Physiotherapy departments / GP surgeries etc may need to be contacted directly for number of attendances. May be appropriate to discuss information required to complete the health economics questionnaire at 6 months so they are aware what information will be required.

6 weeks CCC problems

Consider any problems since application of original cast. Reasons for re-casting such as pain or loss of reduction should be reported as an AE (adverse event). Re-casting due to expected loosening of original cast without loss of reduction are part of normal treatment and usually occurs at 2-3 weeks.

6 months

All should be completed by blinded assessor.

(Researcher to arrange transfer all x-ray images to CD at the end of the 6 month follow up period and send to Oxford Trials Unit by recorded delivery)

14.5 Appendix 5: STUDY FLOW CHART

INCLUSION CRITERIA

- Isolated unstable ankle fracture
- Men or women over 60
- Ambulatory prior to injury (any capacity)
- Capacity to give informed consent
- Capacity to adhere to post operative instructions
- Resident in catchment area of a recruiting hospital
- Able to attend for 6 month follow up

SCREENING

All adults with unstable ankle fractures presenting to hospital over the age of 60

n = 826

with 75% recruitment

RANDOMISE

n = 620

EXCLUSION CRITERIA

- Open fractures
- Insulin dependent diabetes mellitus
- Active leg ulceration
- Established critical leg ischaemia
- Unfit for anaesthesia
- Serious concomitant disease – metastatic disease or terminal illness
- Clinically substantial degenerative or inflammatory arthritis (in the ankle)
- Unable to give informed consent (MMSE <16/30)
- Unwilling to give informed consent

ORIF: n = 310

- Post reduction X-ray
- Mobilise as indicated by surgeon: usually non or partial weight-bearing
- Below knee splintage/no split as normal local practice
- 10 day standard review for removal of sutures
- 6 week review
- 6 month review

10% loss to follow up at 6 months (n = 279)

CLOSE CONTACT CAST: n = 310

- Post reduction X-ray
- Mobilise as indicated by surgeon: usually non-weight-bearing
- Week 1) Review and x-ray in Fracture
- Week 2) Clinic by study investigator for
- Week 3) checking / revision of cast
- 6 week review
- 6 month review

10% loss to follow up at 6 months (n = 279)

Baseline	Theatre	6 weeks	6 - 10 weeks	6 months	Extended Follow up
• Patient information sheet • Consent • X-ray • AO classification • O + M ankle score • Baseline general health • Mental state (MMSE) • Social circumstances • EQ-5D/ SF-12 Quality of Life	• Fluoroscopy • Theatre assessments (including x-ray)	• X-ray • Clinical examination • O+M ankle score • EQ-5D/SF-12 • Patient satisfaction • Health economics Between baseline and 6 weeks: Discussion of semi-structured interviews (sub group of 40 patients, selected sites only)	• Semi-structured interviews with sub group of 40 patients (selected sites only)	• X-ray • Clinical examination Blinded Assessment • O+M ankle score • EQ-5D/SF-12 • 'Get up and Go' test • Patient satisfaction • Health economics	(At least 2 years post treatment) • Postal questionnaire/ telephone interview

UNIVERSITY OF OXFORD

Warwick Medical School
CLINICAL TRIALS UNIT

STATISTICAL ANALYSIS PLAN

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Completion Date: March 2013

Version: 1.1

CONTENT **Page**

DESIGN & AIMS OF THE TRIAL

SECTION 1: DESIGN AND AIMS OF THE TRIAL

1.1 Trial Design

AIM is a pragmatic multi-centre randomised controlled equivalence trial with parallel prospective economic evaluation.

1.2 The Hypothesis

It is hypothesised that the application of the "Close Contact Casting technique (CCC)" for displaced ankle fractures in older adults results in an equivalent outcome compared to the standard care of open surgical reduction and internal fixation (ORIF) in terms of function, complications, quality of life and patient satisfaction with treatment. .

1.3 Clinical Effectiveness

The clinical effectiveness of CCC versus ORIF will be assessed using a functional outcome based on the Olerud & Molander ankle score.

1.4 Radiological Measures

Radiological measurements will be undertaken at screening to classify the fracture, which will also include the clinical evaluation by the admitting surgeon and his team. Measurements will also be taken at 6 weeks and 6 month follow-up to assess fracture and ankle joint congruence.

1.5 Qualitative Study

In order to explore patient experience of their treatment and recovery, a sample of 40 patients will be interviewed using a semi-structured interview schedule between 6-10 weeks post treatment. The recorded interviews of patients from both treatments will be assessed by a qualitative analyst.

1.6 Quality of Life

The quality of life of patients will be assessed at 6 weeks and 6 months after randomisation and will be compared for the two types of ankle injury treatment.

1.7 Health Economics

An economic analysis will be conducted alongside the trial and will include modelling to extrapolate beyond trial data to give cost per quality adjusted life year (QALY) estimates. The analysis also includes: 1) duration of inpatient hospital stay 2) theatre time/implant costs 3) fracture clinic visits 4) additional treatment costs and 5) social dependency/support change at 6 months.

1.8 Harm (Safety) Data

Serious Adverse Events (SAE) associated with either treatment will be compared.

The remainder of the analysis plan has been divided into two main parts:

i) The monitoring of the trial

ii) The main statistical analysis

Section 2 details the monitoring aspects of the trial followed by sections 3 to 9 which detail the final statistical analyses which will be carried out when all the patients have been recruited and the database complete, clean and 'frozen'.

MONITORING OF THE TRIAL

SECTION 2: MONITORING OF THE TRIAL

Monitoring of the trial is a continual process, from the start to the end of the trial. The objectives of the statistical input during trial monitoring are to:

- Give an Overview of the recruitment and follow-up
- Examine the quality of data
- Ensure the protocol is being adhered to
- Assess the randomisation sequence
- Statistical reporting

The Trial Steering Committee (TSC) and the Independent Data Monitoring Committee (DMC) are given the responsibility of monitoring the accumulating data. Statistical reports that provide oversight on the quality of the trial will be produced to cover the following.

2.1 Recruitment and Follow-up

2.1.1 Overall recruitment

The recruitment in the trial will be summarised. Recruitment is continuously assessed by checking whether actual accrual is meeting projected targets, overall and by each centre.

2.1.2 Follow-up Rates

The follow-up rates are based on patient attendance to follow-up clinics, where a health professional will carry out an assessment and complete the study questionnaires.

% Follow-up rate (at time *T*) =

$$\frac{\text{Number of participants assessed at time } T}{\text{Total no.that should have been assessed at time } T} \times 100$$

The follow-up rates will be computed at the following time-points:

- Follow-up at 6 weeks

- Follow-up at 6 months

The template table (Table 6) given in the 'Template tables and figures' section will be used to display the follow-up rates.

2.1.3 Status of Patients

The status of each patient at 6 week and 6 month follow-up will be established to assist in the statistical analysis and in computing the follow-up rates. The status codes will be:

- Completed assessment (in hospital)
- Completed assessment (at home)
- Awaiting assessment
- Lost to follow-up (Didn't attend an assessment)
- Withdrew
- Dead

2.2 Quality of Data

The quality of data in terms of accuracy, completeness, patterns of missing data and number of missing observations, out-of-range values and checking that dates are consecutive from admission through to discharge and follow-up will be summarised to ensure that the database remains clean and accurate.

2.3 Ensuring the trial is conducted according to the protocol

Patients who do not adhere to the protocol and those who withdraw during the trial will be listed. Section 5 defines non-adherence to protocol and section 6 lists the reasons for withdrawal.

2.4 Randomisation

The randomisation procedure will be assessed to ensure that the allocation is correctly stratifying patients in the block strata (centre and fracture pattern) over the two treatments. Fracture pattern is stratified by AO letter with groups "A/B" and "C".

2.5 Statistical Reports

The summaries on the monitoring of the trial in the statistical reports, including a report of missing data, will be provided for the TSC and DMC. The assumptions underlying the sample size estimate will be checked as agreed with the DMC. Details of how the data should be presented (blinded or unblinded) and what summaries should be contained in the closed and open section of the report will be discussed with the DMC

MAIN STATISTICAL ANALYSIS

SECTION 3: SUPERIORITY VERSUS EQUIVALENCE TRIALS

3.1 Superiority trials

- When the objective of a randomised controlled trial is to show the superiority of a new treatment (T) compared to a standard treatment (C), the easiest and most common approach is to conduct a *superiority trial* and subsequently perform a superiority test on the difference in means, denoted by (Δ), between (T) and (C).

- In the case of a (two-sided) superiority trial, the null hypotheses are that treatments are equally effective and the alternative is that they differ- i.e. H_0: Δ=0 and H_A: Δ≠0 respectively.

- In the case of superiority trials, a type I error is falsely finding a treatment effect when there is none, and type II error is failing to detect a treatment effect when truly one exists.

- For superiority trials, intention-to-treat analysis (analysing all patients within their randomised groups, regardless of whether they completed allocated treatment) is recommended. Intention to treat analysis often leads to smaller observed (and more conservative) treatment effects than if patients had adhered to the treatment[1].

3.2 AIM as an equivalence trial

- Based on findings from previous literature, the objective of the AIM trial is to show equal effectiveness of CCC (intervention) and ORIF (standard). It aims to show that the interventions are not different, that they are equally effective or indeed equally ineffective (this is in contrary to an inferiority trial where the objectives are to show that the new treatment is no less effective than the existing one – it may be more or equally effective).

- The primary outcome measure is the Olerud and Molander ankle score at 6 months.

- The Olerud and Molander ankle score is a rating scale from 0 (totally impaired) to 100 (completely unimpaired) and is based on 9 items. The response to each of the 9 items is given as a score and the summation of the scored items makes up the Olerud and Molander ankle score (Olerud C and Molander H, 1984). The score can be categorised into four groupings: 'Poor' (0-30), 'Fair' (31-60), 'Good' (61-90) and 'Excellent' (91-100).

- A margin of equivalence Δ=10% has been chosen by defining the largest difference that is clinically acceptable, so that a difference bigger than this would matter in practice.

- For the OMAS score equivalence limits are based on ± 10% of the expected control mean. This equates to an equivalence region of -6.5 to 6.5 for the difference in scores between the interventions at 6 months.

- For the AIM trial, the null and alternative hypotheses given above are reversed and can be stated as: H_0: $\Delta \leq -\Delta_T$ or $\Delta \geq \Delta_T$ (i.e. $\Delta \neq 0$) and H_A: $-\Delta_T < \Delta < \Delta_T$ (i.e. $\Delta = 0$) where the $-\Delta_T$ and Δ_T are equivalence limits (see figure 1 in section 11).

- The null hypothesis comprises of two hypotheses: H_{01}: $\Delta \leq -\Delta_T$ and H_{02}: $\Delta \geq \Delta_T$ and therefore we have two one-sided tests (each at 2.5% significance level). Both these one-sided tests are rejected at 5% significance level, if and only if $-\Delta_T < \Delta < \Delta_T$. For this reason, our two one-sided tests procedure is a test of size 5%.

- A p-value of less than 5% is indicative of a significance result, and in this case we reject the null hypothesis in favour of the alternative, suggesting that the interventions are equally similar in effectiveness.

- When considering the outcome of a trial that assesses equivalence, the confidence intervals play a critical role. If the two interventions are declared equivalent, the two-sided 95% confidence interval- which defines the range of plausible differences between the two interventions – should lie entirely with the interval $-\Delta_T$ to $+\Delta_T$ - see figure 1 in section 11.

- Just as the null and alternative hypotheses reverse roles, so do the type I/II error rates: type I error rate of equivalence trial is the type II error of the standard comparison (superiority) trial. However, the significance level (alpha) and power (1-beta) i.e. (1-type II error) of the equivalence trial is chosen in the usual manner.

- For the main analysis, using an ITT approach (as done in a superiority trial) sometimes increases the chances of falsely claiming equivalence (inflates the type I error). On the other hand, using a per-protocol approach may bias the treatment in either direction. However, the per-protocol approach is preferred as it protects against the inflation of the type I error rate. It is therefore recommended that a per-protocol analysis be specified as the primary analysis and following this an ITT analysis is conducted with the aim of demonstrating equivalence in both cases.[1,2]

[1] Christensen, E. (2007). "Methodology of superiority vs. equivalence trials and non-inferiority trials." Journal of Hepatology **46**(5): 947-954.
[2] Piaggio, G., D. R. Elbourne, et al. (2006). "Reporting of Noninferiority and Equivalence Randomized Trials." JAMA: The Journal of the American Medical Association 295(10): 1152-1160.

SECTION 4: ANALYSIS POPULATIONS

4.1 Intention to treat and Treatment Received Population

The primary analysis will be the 'per protocol (or treatment received)' analysis. An Intention to treat (ITT) analysis will also be carried out to see if equivalence is demonstrated in either case, as stated in section 3. For the treatment received analysis, only the patients who received their allocated treatment (as defined below) will be analysed and those patients who didn't will be dropped whereas in the ITT analysis all patients will be analysed according to the treatment they were randomised to, irrespective of the treatment they actually received and regardless of whether they have or have not adhered to the protocol (as detailed in section 6).

DEFINITION OF 'RECEIVING ALLOCATED TREATMENT' FOR AIM TRIAL ANALYSIS

	One of these forms for all patients	*Form only if patient returned to theatre during initial admission period*	*Form only if patient was readmitted after initial discharge from hospital*
Allocation:-	**Theatre Primary Procedure Form**	**Theatre Additional Procedure Form**	**Readmission Form**
	Received allocated treatment	n/a	n/a
	Not rec allocated treatment →	Received allocated treatment	n/a
	Not rec allocated treatment →	Not rec allocated treatment →	Received allocated treatment
	Not rec allocated treatment →	n/a →	Received allocated treatment

Question numbers on hard copy CRFs to lift from database that define allocated treatment received or not:

Allocated treatment identified from randomisation data, cross checked against:

THEATRE PRIMARY PROCEDURE FORM

Q2 Date of this primary treatment

Q8 'Did patient receive the treatment allocated by the randomisation service today?' (yes/no response) If allocated treatment indicated, allocated treatment received; if allocated treatment not indicated, allocated treatment not received.

(Q9 provides reason why allocated treatment not received today)

THEATRE ADDITIONAL PROCEDURE FORM

Q2 Date of this additional treatment

Q8 'Actual treatment patient received today' (list of possible treatment options + other box, options include CCC and ORIF).. If allocated treatment indicated, allocated treatment received. If allocated treatment not indicated, allocated treatment not received.

(Q9 provides reason why today's procedure was required)

READMISSION FORM

Q3 Date of surgery in this readmission

Q8 'Actual treatment patient received today' (list of possible treatment options + other box, options include CCC and ORIF). If allocated treatment indicated, allocated treatment received. . If allocated treatment not indicated, allocated treatment not received.

(Q9 provides reason why today's procedure required)

If there is a 'Readmission form' in the database but Q8 is empty, this will be because there was a readmission for some reason but the readmission was NOT due to ankle treatment so any readmission forms with Q8 not completed do not need to be taken into account.

SECTION 5: ANALYSIS DATASETS

There will be two datasets used for the statistical analysis (within each of the analyses stated in section 4): (a) Observed and (b) imputed.

5.1 Observed dataset

This will comprise all the data observed (including follow-up) with missing values. The data will also include a variable to indicate what treatment patients were randomised to and another variable to indicate what treatment they actually received so that the 'ITT' and 'treatment received' analyses can be implemented.

5.2 Imputed dataset

Data will also be imputed to form a dataset to be used for a sensitivity analysis.

Missing item data will be assigned as missing and it may be that the entire score will be missing. For this reason the sensitivity analysis where the items are imputed will prove useful to assess the missingness.

Data can be missing in fields in two situations: (a) when it is not applicable (validly missing) and (b) it can be missing due to patient/health professional leaving fields blank when they should have completed the question with an answer (invalidly missing). The latter will be examined for the different data mechanisms (MAR - missing at random; NMAR - not missing at random; MCAR - missing completely at random) and we will assess whether multiple imputation is viable. In the case where multiple imputation can be used and the data can be assumed normal, multivariate methods will be applied (Little & Rubin, Analysis of Missing data; 1987). In the case where one cannot assume a distribution of the data, the ICE (imputation by chain equations) will be used (www.ats.ucla.edu/stat/stata/library/ice.htm).

If there are only small levels of missing data in the primary outcome simple imputation of maximum and minimum values will be used to check the robustness of results.

SECTION 6: NON-ADHERENCE TO PROTOCOL

There will be some patients who are likely not to adhere to the protocol or depart from the intended treatment and/or evaluation. Any patients that depart from the intended treatment will be because of the treating surgeon's decision; however the patient will still be referred to as having "not adhered" to protocol for the purpose of the analyses. The following list is not by any means complete and during the trial further patients who do not adhere to the protocol will be identified. Currently non-adherence to the protocol consists of:

(i) Withdrawals;

(ii) Ineligible patients: Any patients who were ineligible but were subsequently randomised into the trial;

(iii) Patients who receive an alternative treatment: Any patients who do not receive the allocated treatment (see section 4);

(iv) Incomplete follow up: Any patients who have no follow up data at all.

SECTION 7: WITHDRAWALS

All withdrawals from the trial will be summarised by treatment group.

Withdrawals in this trial will be listed as follows:

- After randomisation but before initial hospital discharge
- After initial hospital discharge but before 6 week follow-up
- After 6 week follow-up but before 6 month follow-up

SECTION 8: EXPLORATORY AND OUTCOME VARIABLES

The following outcomes and variables will be collected in this study.

8.1 Characteristics of Patients and Baseline

Time-point	Variable	Description
Screening	Age	Derived using patients date of birth
	Gender	Patients gender (Male/Female)
	Mini-Mental State Exam (MMSE)	MMSE exam consists of 30 questions to assess cognitive function. The MMSE score is derived by simply summing the number of correct answers (scale 0-30; lower scores represent severe cognitive impairment). Patient eligible if MMSE score is ≥16.
	Affected Side	Side of affected ankle (Right/Left)
	Comminution	Ankle Comminution (Yes/No)
	AO classification	AO fracture classification
Baseline	Olerud and Molander ankle score	The Olerud and Molander ankle score is a rating scale from 0 (totally impaired) to 100 (completely unimpaired) and is based on 9 items. The response to each of the 9 items is given a score and the summation of the scored items makes up the Olerud and Molander ankle score (Olerud C and Molander H, 1984)
	SF-12 Health Survey (Version 1)	Scoring of the SF-12v1 will be carried out using the 'SF-12v2-How to Score version 2 of the SF-12 Health Survey' manual (Ware et al. 1996) which details the scoring of SF-12v1 in Appendix E (p.227). The SF-12 score is on a scale of 0-100; lower scores indicate poorer quality of life
	EQ-5D Scale (day before injury and today)	Evaluates patients quality of life (QOL) based on 5 dimensions converted into a single summary score (scale -0.594 to 1; lower scores indicate worsening health related quality of life). The EQ-5D will be scored using the

		devised algorithm (EuroQol Group, 1990) and summarised as detailed in the User Guide (EuroQol Group, 2005)
	EQ-5D VAS Score (day before injury and today)	Patient indicates best imaginable health state (scale 0-100; higher score indicates a better imaginable health state)
	General health	Patients indicate which statements best describe their health prior to injury and provide general health information (allergies, smoking and alcohol consumption)
	Social Circumstances	Patients information on social circumstances
Randomisation	Age	Derived using patients date of birth
	Gender	Patients gender (Male/Female)
	Affected Side	Side of affected ankle (Right/Left)
	Comminution	Ankle Comminution (Yes/No)
	AO classification letter	AO fracture classification
	AO classification number	AO fracture classification

8.2 Primary, Secondary and Safety Outcomes

Type of Outcome	Time-point	Variable	Description
Primary	6 Weeks and 6 Months	Olerud and Molander ankle score	The Olerud and Molander ankle score is a rating scale from 0 (totally impaired) to 100 (completely unimpaired) and is based on 9 items. The response to each of the 9 items is given a score and the summation of the scored items makes up the Olerud and Molander ankle score (Olerud C and Molander H, 1984). The primary endpoint of this study is the Olerud and Molander score at 6 months.
Safety	Throughout the trial	Serious Adverse Events (SAE)	As given in the protocol

Secondary	6 Weeks	SF-12 Health Survey (Version 1)	Scoring of the SF-12v1 will be carried out using the 'SF-12v2-How to Score version 2 of the SF-12 Health Survey' manual (Ware et al. 1996) which details the scoring of SF-12v1 in Appendix E (p.227). The SF-12 score is on a scale of 0-100; lower scores indicate poorer quality of life
		EQ-5D scale	Evaluates patients quality of life (QOL) based on 5 dimensions converted into a single summary score (scale -0.594 to 1; lower scores indicate worsening health related quality of life). The EQ-5D will be scored using the devised algorithm (EuroQol Group, 1990) and summarised as detailed in the User Guide (EuroQol Group, 2005)
		EQ-5D VAS	Patient indicates best imaginable health state (scale 0-100; higher score indicates a better imaginable health state)
		Assessments of function	Patients range of movement is assessed and date of partial weight bearing is recorded
		Complications	
		Patient satisfaction	Patient indicates how ankle has improved from injury based on a 7 point ordinal scale (very much improved – very much worse), and also their satisfaction with treatment based on a 5 point ordinal scale (very dissatisfied – very satisfied)
	6 Months	SF-12 Health Survey (Version 1)	Scoring of the SF-12v1 will be carried out using the 'SF-12v2-How to Score version 2 of the SF-12 Health Survey' manual (Ware et al. 1996) which details the scoring of SF-12v1 in Appendix E (p.227). The SF-12 score is on a scale of 0-100; lower scores indicate poorer quality of life
		EQ-5D scale	Evaluates patients quality of life (QOL) based on 5 dimensions converted into a single summary score (scale -0.594 to 1; lower scores indicate worsening health related quality of life). The EQ-5D will be scored using the devised algorithm (EuroQol Group, 1990) and summarised as detailed in the User Guide (EuroQol Group, 2005)
		EQ-5D VAS	Patient indicates best imaginable health state (scale 0-100; higher score indicates a better imaginable health state)
		Assessments of function	Patients range of movement, date of partial weight bearing and timed 'Get up and Go' test is assessed

		Complications	
		Patient satisfaction	Patient indicates how ankle has improved from injury based on a 7 point ordinal scale (very much improved – very much worse), and also their satisfaction with treatment based on a 5 point ordinal scale (very dissatisfied – very satisfied)
		Health Economics	

8.3 Tertiary Outcomes and Process Variables

Type of Outcome	**Time-point**	**Variable**	**Description**
Tertiary	CCC Initial Training	Grade of surgeon	Grade of surgeon to be specified (FY2, ST1, ST2, ST3, ST4, ST5, ST6, ST7, ST8, Staff grade, Trust grade, fellow, Consultant or Other)
		Years since qualification	Years since CCST undertaken
		Experience of surgery/casting	Surgeon indicates the number of surgery/casting techniques carried out based on a 7 point ordinal scale (0, 1, 2-5, 6-15, 16-30, 31-50, 51+)
	CCC Further Training	Grade of surgeon	Grade of surgeon to be specified (FY2, ST1, ST2, ST3, ST4, ST5, ST6, ST7, ST8, Staff grade, Trust grade, fellow, Consultant or Other)
		Years since qualification	Years since CCST undertaken
		Experience of surgery/casting	Surgeon indicates the number of surgery/casting techniques carried out based on a 7 point ordinal scale (0, 1, 2-5, 6-15, 16-30, 31-50, 51+)
	Theatre	Anaesthetic Type	Type of anaesthetic given
		American Society of Anaesthesia (ASA) Classification	ASA classification

		Type of Implant	Type of fibula implant used (ORIF only)
		Allocated treatment received	Allocated treatment received (Yes/No)
		Reason allocated treatment not received	Select reason if allocated treatment not received
		Preferred Treatment	Surgeons preferred treatment for patient today
		Adverse events during surgery/manipulation today	Adverse events during surgery/manipulation (Yes/No)
		Grade of Surgeon	Grade of surgeon to be specified (FY2, ST1, ST2, ST3, ST4, ST5, ST6, ST7, ST8, Staff grade, Trust grade, fellow, Consultant or Other)
		Experience of Procedure	Surgeon indicates the number of surgery/casting techniques carried out based on a 7 point ordinal scale (0, 1, 2-5, 6-15, 16-30, 31-50, 51+)
		Consultant supervision	Consultant present today (Yes scrubbed, yes unscrubbed, No)
	Additional Theatre	Visit number	Theatre visit number
		Anaesthetic Type	Type of anaesthetic given
		American Society of Anaesthesia (ASA) Classification	ASA classification
		Type of Implant	Type of fibula and tibia implant used (ORIF only)
		Treatment received today	Select additional treatment received today
		Reason for procedure	Select reason for undertaking procedure
		Adverse events during surgery/manipulation today	Adverse events during surgery/manipulation (Yes/No)
		Result of AE in theatre	If adverse event during surgery/manipulation, what was the result of the adverse event (Death whilst in theatre, life/limb threatening complication in theatre, lead to prolongation of hospitalisation)
	Hospital Discharge	Patient status (Discharged/Died)	Indicate status of patient (discharged/died)

		Post-theatre AE's/complications	Post-theatre AE's or complications highlighted from list, if any
		Patient re-admitted to theatre	Patient readmitted to theatre at any point (Yes/No)
		Number of CCC applications	Specify total number of CCC applications in plaster room and in theatre
	Hospital Readmission	Reason for readmission	Reason for readmission (surgical/manipulation, medical/surgical, other)
		Anaesthetic Type	Type of anaesthetic given
		American Society of Anaesthesia (ASA) Classification	ASA classification
		Type of Implant	Type of fibula and tibia implant used (ORIF only)
		Treatment received today	Select treatment received today
		Reason for visit to theatre	Select reason for undertaking procedure
		AE's/Complications in theatre	Adverse events during surgery/manipulation (Yes/No)
		Result of AE in theatre	Adverse event during surgery/manipulation, what was the result of the adverse event (Death whilst in theatre, life/limb threatening complication in theatre, lead to prolongation of hospitalisation)
		AE's/Complications post-theatre	Adverse events after surgery/manipulation (Yes/No)
		Result of AE post-theatre	Adverse event during surgery/manipulation, what was the result of the adverse event (Life/limb threatening complication in theatre, lead to prolongation of hospitalisation)
		Re-admission to remove syndesmosis screws	Was re-admission to remove syndesmosis screws (Yes/No)
		Readmission unrelated to study ankle	
		Patient status at the end of hospital readmission episode	Status of patients after hospital readmission episode (Discharged/Died)
	Withdrawal	Patient expressed wish to withdraw	Patient expressed wish to withdraw (Yes/No), stating reason
		Patient withdrawn by surgeon	Patient withdrawn by surgeon (Yes/No), stating reason
		If patient withdrew, level of withdrawal	Indicate level of withdrawal of patient

		Timing of withdrawal	Indicate the time point when the patient withdrew or was withdrawn from the trial
Process	Screening	Time from Injury to Screening	Date of Screening – Date of Injury (as recorded on the Screening Form)
	Randomisation/Theatre	Time from randomisation to Theatre Procedure	Date of Treatment (as recorded on the Theatre Primary Procedure Form) – Date of randomisation (as recorded on the Randomisation Form)
	Theatre	Time from entry into anaesthetic room to Start time in theatre	Start time in theatre - Time into anaesthetic room (as recorded on the Theatre Primary Procedure Form)
		Time from Start of procedure in theatre to End of procedure in theatre	End time in theatre - Start time in theatre (as recorded on the Theatre Primary Procedure Form)
	Additional Theatre Procedure	Time from Primary procedure in theatre to Additional procedure in theatre	Date of Treatment (as recorded on the Additional Procedure in Theatre Form) – Date of Treatment (as recorded on the Primary Procedure in Theatre Form)
		Time from entry into anaesthetic room to Start time in theatre	Start time in theatre - Time into anaesthetic room (as recorded on the Additional Procedure in Theatre Form)
		Time from Start of procedure in theatre to End of procedure in theatre	End time in theatre - Start time in theatre (as recorded on the Additional Procedure in Theatre Form)
	Theatre/Hospital Discharge	Time from Theatre procedure to Hospital discharge	Date of hospital discharge (as recorded on the Hospital Discharge Form) – Date of Treatment (as recorded on the Theatre Primary Procedure Form)
	Hospital Discharge/Hospital Readmission	Time from Hospital discharge to Hospital Readmission	Date of Hospital readmission (as recorded on the Hospital Readmission Form) – Date of Hospital discharge (as recorded on the Hospital Discharge Form).

SECTION 9: STATISTICAL ANALYSIS AND PRESENTATION OF THE RESULTS

Clinical equivalence studies are usually one-sided – the AIM trial has been designed to show that CCC is not worse than ORIF by a difference of 10%. All statistical tests will be performed at the 5% significance level.

The statistical analyses will be carried out using STATA (version 12).

The statistical report for the study will follow the guidelines set by CONSORT for reporting of equivalence and non-inferiority randomised trials (2006). The report will detail the design, conduct, analysis and results of the data. This report will be supported by the tables, plots and flow diagrams that have been included at the end of this section.

9.1 Patient Flow

The flow of patients throughout the trial will be illustrated using the CONSORT diagram, as shown in Figure 1.

9.2 Recruitment

The recruitment of patients into the trial will be summarised by the CONSORT diagram (Figure 1) and by Tables 1 to 5, which will present the following information respectively:

- the number (%) of patients in the trial that have been screened, randomised, followed up, withdrawn and non-attendees

- the number (%) of withdrawals throughout the trial will be summarised by treatment group

- the number (%) of the withdrawal details will be summarised by treatment group

- the number (%) of non-attendees during follow-up will be summarised by treatment group

- the number (%) of patients not receiving the allocated treatment will be summarised by treatment group

The number (%) of patients at each follow-up time point will be summarised in terms of response status i.e. completed follow-up, withdrawn, non-attendee etc., as shown in table 6. The above statistics will be monitored at the centre level for internal reasons only.

9.3 Randomisation

The number of patients randomised and not randomised has been detailed in Table 1. The randomisation of all eligible patients will be summarised in Tables 7 and 8, which will present the following information respectively:

- the number (%) of patients randomised to each treatment group will be summarised for each centre

- the number (%) of patients randomised to each treatment group will be summarised by randomisation strata (recruiting site and fracture pattern)

9.4 Baseline Data

The baseline demographic and clinical characteristics of all randomised patients will be summarised by treatment group in Tables 9 to 14.

9.5 Harm Data (Serious Adverse Events)

The number (%) of Serious Adverse Events (SAE's) will be summarised by treatment group in Tables 15, 16 and 17.

9.6 Learning and Expertise Analyses

Data collected during initial and further CCC training will be analysed to establish the extent, if any, of learning or expertise effects. It is common practice that surgeons have particular expertise in selected techniques, and for surgical teams to organise their workloads so that expertise is utilised to best effect. This study will not interfere with this dynamic. It is

therefore not easy to anticipate the direction of expertise and learning effects. For each surgeon participating in the study, the following information is collected: historical experience and preferences for ORIF and casting, grade of surgeon, time since qualification as a surgeon, time since first operation on the study. This data will be summarised by recruitment centre and analysed for evidence of learning and expertise effects.

9.7 Post Randomisation and Follow-up

(a) Primary outcome measure

The Olerud and Molander (O&M) Ankle Score is the primary outcome measure in the study and will be collected at 6 weeks and 6 months, with 6 months being the primary endpoint.

Table 18 summarises the O&M ankle score at 6 weeks and 6 months by treatment group. The 95% confidence interval for the difference between the two scores on the interventions will be used to decide on equivalence. The 6 month O&M ankle score will then be compared between treatment groups using a linear regression model, with the dependent variable being the 6 month O&M ankle score and the independent variables as treatment and any other important predictors (e.g. baseline score, age, gender and centre). A figure showing confidence intervals and margins of equivalence will also be presented. A longitudinal analysis will also be carried out using longitudinal regression techniques to obtain a single estimate of treatment over the 6 month period. The variance-covariance matrix of the residuals will be assessed to determine the structure of the variation over time (compound symmetry, constant variance etc.). The time and treatment covariance along with the other covariates will be entered into the model.

(b) Secondary, tertiary and process variables

Secondary, tertiary and process variables for initial, further CCC training and from randomisation to follow-up will be summarised in tables 19-28. These variables are of three different types and will be analysed as followed:

Categorical data – will be analysed using logistic regression models, with treatment group as an independent variable along with other important predictors. Summary statistics will be based on proportions.

Continuous data – will be analysed using linear regression models, with treatment group as an independent variable along with other important predictors (e.g. age, gender and centre). Treatment group difference will be based on estimates of the adjusted means and 95% CI's. The primary outcome measure will be based on this type of analysis.

Time to event data - Time to event data (e.g. time to discharge) will be analysed using a log-rank test. Any patients who have not experienced an event at the time point of interest or withdrawn will be censored. The proportion in each treatment group experiencing an event over time will be illustrated using a Kaplan-Meier curve. The p-value and a hazard ratio with its 95% CI from a Cox proportional hazards model will also be presented. The proportional hazards assumption across treatment arms will be checked graphically using a log-cumulative hazard plot.

SECTION 10: HEALTH ECONOMIC STATISTICAL ANALYSIS PLAN

This section describes the approach to the health economic analysis.

10.1 Perspectives for the analysis

Two perspectives will be explored within the economic analyses: (a) NHS & Personal Social Services Perspective and (b) Societal perspective.

10.1.1 NHS & Personal Social Services Perspective

In common with the NICE reference case, the base case perspective for the economic analysis will relate to those costs borne by the National Health Service and Personal Social Services in the UK. Other aspects of the NICE reference case, such as the use of a preference based utility measure for QALY estimation, and the discounting of both resource use costs and health outcomes at a rate of 3.5% will be adopted.

10.1.2. Societal perspective

The broader societal perspective will be explored by considering direct patient costs as well as potential productivity (indirect) cost estimates in addition to those falling on the NHS and Personal Social Services.

10.2. Data preparation

Data collected within the AIM trial relate to resource use (medical care, social care, patient related as well as employment) and to health outcome measures (mortality and quality of life as measured by the EQ-5D instrument). In order to estimate costs and preference based health related quality of life data, appropriate weights need to be employed in the form of unit cost data and HRQoL tariffs.

10.2.1. Unit cost information

Unit cost data for health care medical resource use will be taken from standard sources, such as the NHS reference costs and PSSRU Costs of Health & Social Care (REF). Patient costs will be based on patient self-report and productivity losses will be based on the average wage rate.

10.2.2. Health related Quality of Life Utilities

Utility weights for the EQ-5D algorithm will be generated from the MVH survey conducted in a random sample of the UK population (Dolan et al 1997).

10.3. Cost-effectiveness analyses

Three different approaches to cost-effectiveness estimation will be presented based on the observed time period and approach to modelling: (a) aggregate comparison between CCC and ORIF in terms of cost and QALYs based on the six month follow-up of the trial; (b) statistical models of cost and effect for the six months follow-up of the trial; (c) extrapolation of the statistical modelling to patient lifetimes.

10.3.1 Aggregate comparative analysis

The resource costs and HRQoL data will be assembled at the level of the individual patient using the weights described in 9.2 above. Mean costs and mean QALYs will then be calculated for the six-month follow-up of the trial and comparative (incremental) cost, QALY and cost-effectiveness will be calculated between the CCC and ORIF arms of the trial.

10.3.2. Statistical modelling of observed data

Statistical regression models will be fit to the cost and HRQoL data using the flexible framework of generalised linear modelling (GLM) that is able to handle the skewness that is often present in these data.[3] The statistical modelling of the data will allow adjustment for any imbalance in baseline variables, as well as exploration of potential prognostic and predictive factors in line with the statistical analysis of the clinical data described in Section 9.7 above.

10.3.3. Extrapolation beyond the data

The statistical models from 10.3.2 will be used to form the basis of an extrapolation to patient lifetimes by projecting forward the parametric cost and HRQoL equations. Two adaptations will be considered at this point. Firstly, the possible inclusion of a time trend variable in each equation will be explored. Secondly, standard age-sex adjusted survival

[3] For HRQoL, which is often subject to left skew, the simple X = 1 – HRQoL linear transformation will be employed and GLMs used to model the right skew on this 'utility decrement' scale.

curves will be used to weight the future predictions to ensure that realistic lifetime cost and QALY estimates are achieved.

10.4 Presentation of results

Care will be taken to ensure that all cost, QALY and cost-per-QALY estimates presented are accompanied by appropriate estimates of uncertainty. For the analysis of patient level data within the observed trial period, the appropriate statistical analysis based on estimated standard errors. For the extrapolated results, the statistical measures of uncertainty will be combined with scenario analyses exploring the sensitivity of the results to different extrapolation assumptions.

For costs, QALYs, and incremental costs and QALYs, standard errors and confidence intervals will be presented based on non-parametric bootstrapping. For cost-effectiveness results, non-parametric bootstrap replications of cost and effect differences will be presented on the cost-effectiveness plane. Uncertainty will be summarised using acceptability curves.

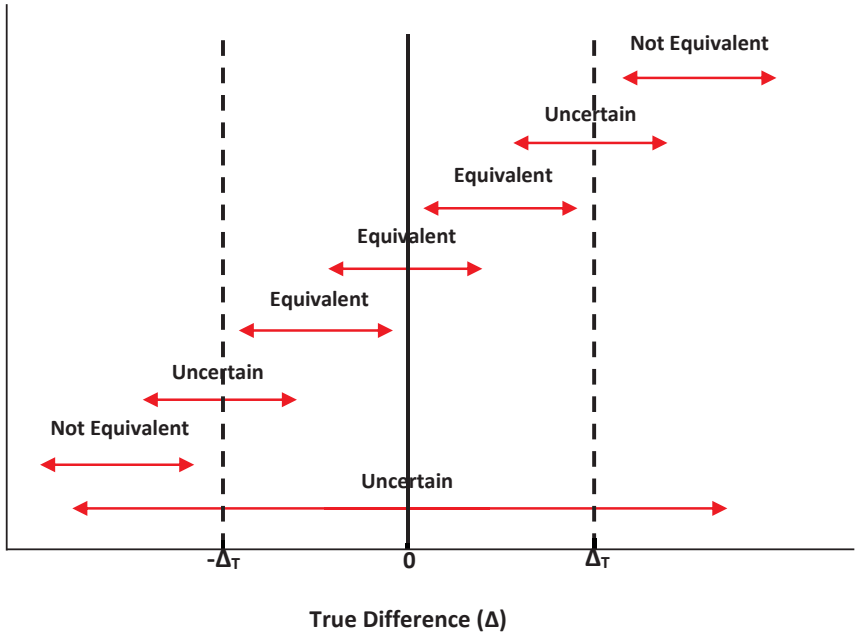
In addition to net-cost results – disaggregated costs by component of cost will be presented. In particular, the cost differences between the two procedures and the existence of any statistically significant cost-offsets to those procedures will be explored.

SECTION 11: INTERPRETATION OF THE RESULTS

As AIM is an equivalence trial, a significant result ($p< 0.05$) means that the two treatments are equivalent.

Ideally we want to reject the null hypothesis using an appropriate statistical test (use the t-test for the primary outcome for the AIM trial) and conclude that there is statistically significant evidence that treatments (ORIF) and (CCC) are equivalent. If the true treatment difference along with its 95% CI overlaps either the upper or lower limits (i.e. overlaps either $-\Delta_T$ or Δ_T) then there is no certainty as to whether the treatments have equal effectivenss and if it lies completely outside the interval $[-\Delta_T, \Delta_T]$ then the treatments are not equivalent. The several possible outcomes from an equivalence trial can be better understood graphically using the CI approach as shown in Figure 1. Although the usual hypothesis test can be applied, the preferred approach for an equivalence trial is to use the CI interval approach.2

Figure 1 – Examples of possible outcomes from an equivalence trial using the confidence interval approach where $[-\Delta_T, \Delta_T]$ is the pre-specified equivalence range.



TEMPLATE TABLES AND FIGURES

Figure 1: CONSORT diagram for the AIM Trial

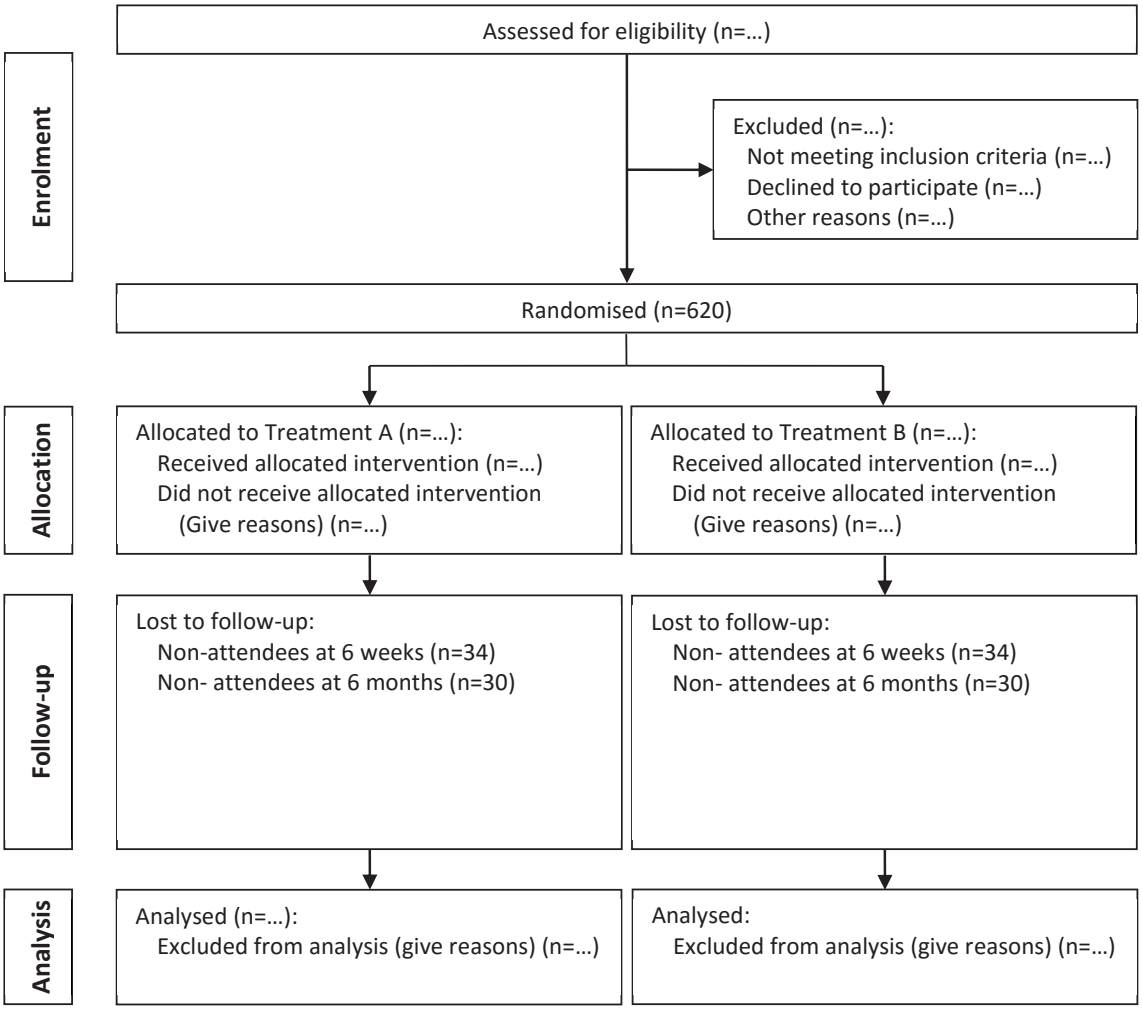


Table 1: Flow of patients in the AIM trial

FROM SCREENING TO PRE-RANDOMISATION	All patients screened	n (%)
	Excluded Patients: Patients not meeting inclusion criteria	n (%)
	Excluded Patients: Patients meeting inclusion criteria but also meet at least one of the exclusion criteria. Exclusion criteria includes MMSE<16.	n (%)
PRE-RANDOMISATION	Patients with baseline data	n (%)
RANDOMISATION	Patients satisfying the inclusion criteria – RANDOMISED	n (%)
	Patients satisfying the inclusion criteria – NOT RANDOMISED	n (%)
	Patient randomised but ineligible	n (%)
FOLLOW-UP	No follow-up data at any time point	n (%)
	Follow-up data at 6 weeks only	n (%)
	Follow-up data at 6 months only	n (%)
	Follow-up data at all time points	n (%)
DIED	After randomisation but before theatre for treatment	n (%)
	In theatre but before starting any trial procedure	n (%)
	During initial treatment in theatre	n (%)
	In hospital ≤30 days following initial treatment in theatre	n (%)
	In hospital >30 days following initial treatment in theatre	n (%)

	After initial hospital discharge ≤30 days after initial treatment but before 6 week follow-up	n (%)
	After initial hospital discharge >30 days after initial treatment but before 6 week follow-up	n (%)
	After 6 week follow-up but before 6 month follow-up	n (%)
WITHDRAWALS	After randomisation but before hospital discharge	n (%)
	After hospital discharge but before 6 week follow-up	n (%)
	After 6 week follow-up but before 6 month follow-up	n (%)
NON-ATTENDEES (follow-up)	At 6 weeks follow-up	n (%)
	At 6 month follow-up	n (%)

Table 2: Timing of withdrawal summarised by treatment group

		ORIF	CCC	TOTAL
WITHDRAWALS	After randomisation but before hospital discharge	n (%)	n (%)	N
	After hospital discharge but before 6 week follow-up	n (%)	n (%)	N
	After 6 week follow-up but before 6 month follow-up	n (%)	n (%)	N
	Missing	n (%)	n (%)	N

Table 3: Withdrawal details summarised by treatment group

		ORIF	CCC	TOTAL	P-value
Patient requested to withdraw from Trial	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Surgeon caring for patient requested for patient to be withdrawn	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Patient level of withdrawal	Not stated	n (%)	n (%)	N	xx.xx
	No objection to study using data collected up to withdrawal	n (%)	n (%)	N	
	No objection to tracking overall health status via official databases (no patient contact)	n (%)	n (%)	N	
	Objects to study using data collected up to withdrawal	n (%)	n (%)	N	
	Objects to study tracking health status via official databases (no patient contact)	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Listing 1: If patient expressed wish to withdraw and reason known, please specify reason below

Listing of reasons will be by treatment group. The following will be listed: Patient number, centre, timing of withdrawal and reason for withdrawal.

Listing 2: If surgeon caring for patient requested for the patient to be withdrawn, please specify reason below

Listing of reasons will be by treatment group. The following will be listed: Patient number, centre, surgeons name, timing of withdrawal and reason for withdrawal.

Table 4: Non-attendees during follow-up summarised by treatment group

	ORIF	CCC	TOTAL	P-value
At 6 weeks follow-up	n (%)	n (%)	N	xx.xx
At 6 month follow-up	n (%)	n (%)	N	xx.xx

Table 5: Patients who did not receive allocated treatment summarised by treatment group

(What is not receiving allocated treatment: patient did not receive allocated treatment will be viewed across the same three treatment forms as for defining those who did receive allocated treatment (Theatre Primary Procedure Form, Theatre Additional Procedure Form, Readmission Form) –see section 5).

		ORIF	CCC	TOTAL	P-value
If patient did not receive allocated treatment, what treatment did they receive	Traditional plaster cast	n (%)	n (%)	N	xx.xx
	External fixation	n (%)	n (%)	N	
	Retrograde nail	n (%)	n (%)	N	
	ORIF	n (%)	n (%)	N	
	CCC	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Reason why ORIF not received if patient allocated to ORIF	Ankle too swollen for surgery	n (%)	n (%)	N	xx.xx
	Poor skin condition for surgery	n (%)	n (%)	N	
	Fracture blisters	n (%)	n (%)	N	
	Poor quality or fragmented bone	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Reason why CCC not received if patient allocated to CCC	Ankle too swollen for surgery	n (%)	n (%)	N	xx.xx
	Fracture proved irreducible by closed manipulation	n (%)	n (%)	N	
	Unable to maintain/retain reduction	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Listing 3: If patient did not receive allocated treatment and received 'Other' treatment, please specify

Listing of 'other' treatment received will be summarised by allocated treatment group. The following will be listed: Patient number, centre and specification of 'other' treatment given.

Listing 4: If patient allocated to ORIF, why did they not receive ORIF. If 'other' reason, please specify

The following will be listed: Patient number, centre and 'other' reason why ORIF not received.

Listing 5: If patient allocated to CCC, why did they not receive CCC. If 'other' reason, please specify

The following will be listed: Patient number, centre and 'other' reason why CCC not received.

Table 6: Follow-up rates in the AIM Trial

	6 Weeks	6 Months
Completed assessment (in hospital)	n (%)	n (%)
Completed assessment (at home)	n (%)	n (%)
Completed assessment (over telephone)	n (%)	n (%)
Non-attendee	n (%)	n (%)
• Lost to follow-up	n (%)	n (%)
• Withdrawn	n (%)	n (%)
• Dead	n (%)	n (%)

Table 7: Randomised patients summarised by treatment group and centre

	ORIF	CCC	TOTAL
John Radcliffe, Oxford	n (%)	n (%)	N
Frenchay, Bristol	n (%)	n (%)	N
⋮	⋮	⋮	⋮

Table 8: Randomised patients summarised by randomisation strata (recruiting site and fracture pattern)

FRACTURE PATTERN	A+B		C	
	ORIF	CCC	ORIF	CCC
John Radcliffe, Oxford	n (%)	n (%)	n (%)	n (%)
Frenchay, Bristol	n (%)	n (%)	n (%)	n (%)
⋮	⋮	⋮	⋮	⋮

Table 9: Baseline demographic and clinical characteristics of all randomised patients summarised by treatment group

		ORIF	CCC	TOTAL
Age (years)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Gender	Male	n (%)	n (%)	N
	Female	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Olerud and Molander Ankle Score	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
SF-12 Mental	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
SF-12 Physical	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D Mobility (day before injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)

	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Self-care (day before injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Usual activities (day before injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Pain/discomfort (day before injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Anxiety/depression (day before injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Score (Day before injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D VAS (Day before injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D Mobility (Today)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Self-care	Level 1	n (%)	n (%)	n (%)

(Today)	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Usual activities (Today)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Pain/discomfort (Today)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Anxiety/depression (Today)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Score (Today)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D VAS (Today)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx

Table 10: General Health Question – 'Did you have the problem?' summarised by treatment group

		ORIF	CCC	TOTAL
Heart Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Hypertension	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Asthma/COPD	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Diabetes	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Parkinsons	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Epilepsy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Renal Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Liver Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
CVA/TIA	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Peptic Ulcer	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Malignancy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
DVT/PE	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Osteoarthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Rheumatoid Arthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Depression	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Dementia	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N

Listing 6: If patient had any other medical problems, please specify

The following will be listed: Patient number, centre and other medical problems.

Table 11: General Health Question – 'Did you receive treatment for it?' summarised by treatment group

		ORIF	CCC	TOTAL
Heart Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Hypertension	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Asthma/COPD	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Diabetes	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Parkinsons	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Epilepsy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Renal Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Liver Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
CVA/TIA	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Peptic Ulcer	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Malignancy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
DVT/PE	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Osteoarthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Rheumatoid Arthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Depression	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Dementia	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N

Table 12: General Health Question – 'Did it limit your activities?' summarised by treatment group

		ORIF	CCC	TOTAL
Heart Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Hypertension	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Asthma/COPD	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Diabetes	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Parkinsons	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Epilepsy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Renal Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Liver Disease	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
CVA/TIA	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Peptic Ulcer	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Malignancy	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
DVT/PE	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Osteoarthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Rheumatoid Arthritis	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Depression	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Dementia	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N

Table 13: General health (continued) summarised by treatment group

		ORIF	CCC	TOTAL
Allergies	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Smoking	Yes	n (%)	n (%)	N
	Never	n (%)	n (%)	N
	Ex-smoker	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
If ex-smoker, how many years since stopping	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
If yes or ex-smoker, how many smoked on average per day	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
If yes or ex-smoker, total number of years as a smoker	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Number of units of alcohol in an average week	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx

Listing 7: If patient has known allergies, please specify type of allergy

The following will be listed: Patient number, centre and type of allergy.

Table 14: Social Circumstances of all randomised patients summarised by treatment group

		ORIF	CCC	TOTAL
Admitted from	Own home	n (%)	n (%)	N
	Warden accommodation	n (%)	n (%)	N
	Residential home	n (%)	n (%)	N
	Nursing home	n (%)	n (%)	N
	Rehabilitation	n (%)	n (%)	N
	Acute hospital	n (%)	n (%)	N
	Community hospital	n (%)	n (%)	N
	Temporary residence	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Home Support	Lives alone	n (%)	n (%)	N
	Lives with someone	n (%)	n (%)	N
	Lives with carers	n (%)	n (%)	N
	Home care package	n (%)	n (%)	N
	Institution care	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Usual walking aids	None	n (%)	n (%)	N
	One stick	n (%)	n (%)	N
	Two sticks	n (%)	n (%)	N
	Frame/Rollator	n (%)	n (%)	N
	Wheelchair	n (%)	n (%)	N

	Missing	n (%)	n (%)	N
Using appropriate aid, how far can you walk	About House	n (%)	n (%)	N
	<100m	n (%)	n (%)	N
	<1/2 mile	n (%)	n (%)	N
	>1/2 mile	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
What limits your mobility	Nothing	n (%)	n (%)	N
	Pain	n (%)	n (%)	N
	Breathlessness	n (%)	n (%)	N
	Other	n (%)	n (%)	N
	Missing	n (%)	n (%)	N

Listing 8: What limits your mobility. If other, please specify

The following will be listed: Patient number, centre and other things limiting the patient's mobility.

Table 15: Serious Adverse Events (SAE's) summarised by treatment group

	ORIF	CCC	TOTAL
Reason: Death within 30 days of trial treatment	n (%)	n (%)	N
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Death related to the trial surgical intervention at	n (%)	n (%)	N

any time			
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: A life or limb threatening complication	n (%)	n (%)	N
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Prolongation of existing hospitalisation	n (%)	n (%)	N
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N

Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Re-hospitalisation for any ankle fracture treatment (trial ankle)	n (%)	n (%)	N
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Other medically significant reason for reporting	n (%)	n (%)	N
Location of event			
In hospital after randomisation but prior to trial treatment	n (%)	n (%)	N
In theatre prior to treatment	n (%)	n (%)	N
In theatre during/following treatment	n (%)	n (%)	N
Post theatre as inpatient (initial inpatient episode)	n (%)	n (%)	N
After discharge from hospital	n (%)	n (%)	N
During hospital re-admission for ankle related surgery/treatment	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N

Listing 9: Other medically significant reason for reporting. If so, please specify

The following will be listed: Patient number, centre and specified reason.

Table 16: Reason for reporting a SAE summarised by patient's current status and treatment group

	ORIF	CCC	TOTAL
Reason: Death within 30 days of trial treatment			
Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Death related to the trial surgical intervention at any time			
Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: A life or limb threatening complication			
Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Prolongation of existing hospitalisation			
Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Re-hospitalisation for any ankle fracture treatment (trial ankle)			

Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N
Reason: Other medically significant reason for reporting			
Current status			
Recovered	n (%)	n (%)	N
Under treatment	n (%)	n (%)	N
Deceased	n (%)	n (%)	N
Unknown	n (%)	n (%)	N
Other	n (%)	n (%)	N
Missing	n (%)	n (%)	N

Listing 10: If patient's current status is specified as 'other', please specify

The following will be listed: Patient number, centre and specified other current status.

Table 17: Principal Investigator's assessment of SAE's summarised by treatment group

	ORIF	CCC	TOTAL
Expected	n (%)	n (%)	N
Unexpected	n (%)	n (%)	N
SAE caused by taking part in AIM	n (%)	n (%)	N
SAE not caused by taking part in AIM	n (%)	n (%)	N
Missing	n (%)	n (%)	N

Listing 11: If SAE caused by taking part in the AIM trial, please specify

Listing will be by treatment group. The following will be listed: patient number, specification, person making judgement and their position

Table 18: Primary outcome at 6 weeks and 6 months summarised by treatment group

			ORIF	CCC	TOTAL	Statistics (95% CI)
Olerud and Molander Ankle Score	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	

Figure 2: Observed treatment difference plot with 95% confidence interval

Table 19: Initial CCC training summarised by recruiting Centre

		CENTRES			
		John Radcliffe, Oxford	**Frenchay, Bristol**	**…**	**TOTAL**
Grade of Surgeon	FY2	n (%)	n (%)	…	N
	ST1	n (%)	n (%)	…	N
	ST2	n (%)	n (%)	…	N
	ST3	n (%)	n (%)	…	N
	ST4	n (%)	n (%)	…	N
	ST5	n (%)	n (%)	…	N
	ST6	n (%)	n (%)	…	N
	ST7	n (%)	n (%)	…	N
	ST8	n (%)	n (%)	…	N
	Staff Grade	n (%)	n (%)	…	N

	Trust Grade	n (%)	n (%)	…	N
	Fellow	n (%)	n (%)	…	N
	Consultant	n (%)	n (%)	…	N
	Other	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
CCST undertaken	Yes	n (%)	n (%)	…	N
	No	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
IF CCST undertaken, years since undertaken	Mean	xx.xx	xx.xx	…	xx.xx
	N	xx.xx	xx.xx	…	xx.xx
	Std. Deviation	xx.xx	xx.xx	…	xx.xx
	Median	xx.xx	xx.xx	…	xx.xx
	Minimum	xx.xx	xx.xx	…	xx.xx
	Maximum	xx.xx	xx.xx	…	xx.xx
	Missing	xx.xx	xx.xx	…	xx.xx
Number of CCC techniques carried out as at TODAY	0	n (%)	n (%)	…	N
	1	n (%)	n (%)	…	N
	2-5	n (%)	n (%)	…	N
	6-15	n (%)	n (%)	…	N
	16-30	n (%)	n (%)	…	N
	31-50	n (%)	n (%)	…	N
	51+	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Number of ORIF techniques carried out as at TODAY	0	n (%)	n (%)	…	N
	1	n (%)	n (%)	…	N
	2-5	n (%)	n (%)	…	N
	6-15	n (%)	n (%)	…	N
	16-30	n (%)	n (%)	…	N
	31-50	n (%)	n (%)	…	N
	51+	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Involved in Ankle feasibility Study (John Radcliffe only)	Yes	n (%)	n (%)	…	N
	No	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Does surgeon have a general treatment preference	Yes	n (%)	n (%)	…	N
	No	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N

If yes, which treatment is preferred	ORIF	n (%)	n (%)	…	N
	CCC	n (%)	n (%)	…	N
	Other	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N

Table 20: Further CCC training summarised by recruiting Centre

		CENTRES			
		John Radcliffe, Oxford	**Frenchay, Bristol**	**…**	**TOTAL**
Grade of Surgeon	FY2	n (%)	n (%)	…	N
	ST1	n (%)	n (%)	…	N
	ST2	n (%)	n (%)	…	N
	ST3	n (%)	n (%)	…	N
	ST4	n (%)	n (%)	…	N
	ST5	n (%)	n (%)	…	N
	ST6	n (%)	n (%)	…	N
	ST7	n (%)	n (%)	…	N
	ST8	n (%)	n (%)	…	N
	Staff Grade	n (%)	n (%)	…	N
	Trust Grade	n (%)	n (%)	…	N
	Fellow	n (%)	n (%)	…	N
	Consultant	n (%)	n (%)	…	N
	Other	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Number of CCC techniques carried out as at TODAY	0	n (%)	n (%)	…	N
	1	n (%)	n (%)	…	N
	2-5	n (%)	n (%)	…	N
	6-15	n (%)	n (%)	…	N
	16-30	n (%)	n (%)	…	N
	31-50	n (%)	n (%)	…	N
	51+	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Number of ORIF techniques carried out as at TODAY	0	n (%)	n (%)	…	N
	1	n (%)	n (%)	…	N
	2-5	n (%)	n (%)	…	N
	6-15	n (%)	n (%)	…	N
	16-30	n (%)	n (%)	…	N
	31-50	n (%)	n (%)	…	N
	51+	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N
Does surgeon have a general treatment	Yes	n (%)	n (%)	…	N
	No	n (%)	n (%)	…	N

preference	Missing	n (%)	n (%)	…	N
If yes, which treatment is preferred	ORIF	n (%)	n (%)	…	N
	CCC	n (%)	n (%)	…	N
	Other	n (%)	n (%)	…	N
	Missing	n (%)	n (%)	…	N

Table 21: Primary Theatre procedure summarised by treatment group

		ORIF	CCC	TOTAL	P-value
Anaesthetic type	General	n (%)	n (%)	N	xx.xx
	Regional	n (%)	n (%)	N	
	Spinal	n (%)	n (%)	N	
	Epidural	n (%)	n (%)	N	
	Regional and general	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
ASA classification	1	n (%)	n (%)	N	xx.xx
	2	n (%)	n (%)	N	
	3	n (%)	n (%)	N	
	4	n (%)	n (%)	N	
	5	n (%)	n (%)	N	
	Not stated	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Implant type (ORIF only): Fibula	Screws	n (%)	_	N	-
	Anti-glide plate	n (%)	_	N	
	1/3 tubular plate	n (%)	_	N	
	Dynamic Compression Plate	n (%)	_	N	
	Reconstruction Plate	n (%)	_	N	
	Locking Compression Plate	n (%)	_	N	
	Other Plate	n (%)	_	N	
	Tightropes	n (%)	_	N	
	Tension-band wires	n (%)	_	N	
	Other wires	n (%)	_	N	
	Missing	n (%)	_	N	
Implant type (ORIF only): Tibia	Screws	n (%)	_	N	-
	Plate type	n (%)	_	N	
	Tension-band wires	n (%)	_	N	

	Other wires	n (%)	_	N	
	Missing	n (%)	_	N	
Did patient receive allocated treatment	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Listing 12: Other Anaesthetic type

Listing will be by treatment group. The following will be listed: patient number and type of other anaesthetic

Listing 13: Other implant plate (ORIF only)-Fibula

The following will be listed: patient number and type of other plate

Listing 14: Other implant wires (ORIF only)-Fibula

The following will be listed: patient number and type of other wire

Listing 15: Other implant plate (ORIF only)-Tibia

The following will be listed: patient number and type of other plate

Listing 16: Other implant wires (ORIF only)-Tibia

The following will be listed: patient number and type of other wire

Table 22: Preferred treatment for primary theatre procedure summarised by treatment group

		ORIF	CCC	TOTAL	P-value
Preferred treatment for patient today	Traditional plaster cast	n (%)	n (%)	N	xx.xx
	External fixation	n (%)	n (%)	N	
	Retrograde nail	n (%)	n (%)	N	
	ORIF	n (%)	n (%)	N	
	CCC	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Any adverse events/complications during surgery/manipulation today	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Listing 17: Other preferred treatment for primary theatre procedure

Listing will be by treatment group. The following will be listed: patient number and type of other preferred treatment for primary theatre procedure

Table 23: Experience of surgeon conducting primary theatre procedure summarised by treatment group

		ORIF	CCC	TOTAL	P-value
Grade of operating surgeon	FY2	n (%)	n (%)	N	xx.xx
	ST1	n (%)	n (%)	N	
	ST2	n (%)	n (%)	N	
	ST3	n (%)	n (%)	N	
	ST4	n (%)	n (%)	N	
	ST5	n (%)	n (%)	N	
	ST6	n (%)	n (%)	N	
	ST7	n (%)	n (%)	N	
	ST8	n (%)	n (%)	N	
	Staff Grade	n (%)	n (%)	N	
	Trust Grade	n (%)	n (%)	N	
	Fellow	n (%)	n (%)	N	
	Consultant	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Grade of most senior surgeon present	FY2	n (%)	n (%)	N	xx.xx
	ST1	n (%)	n (%)	N	
	ST2	n (%)	n (%)	N	
	ST3	n (%)	n (%)	N	
	ST4	n (%)	n (%)	N	
	ST5	n (%)	n (%)	N	
	ST6	n (%)	n (%)	N	
	ST7	n (%)	n (%)	N	
	ST8	n (%)	n (%)	N	
	Staff Grade	n (%)	n (%)	N	
	Trust Grade	n (%)	n (%)	N	
	Fellow	n (%)	n (%)	N	
	Consultant	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Table 24: Outcomes at follow-up (6 weeks and 6 months) summarised by treatment group

			ORIF	CCC	TOTAL	P-value
SF-12 (Mental)	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
SF-12 (Physical)	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
EQ-5D (Mobility)	**6 weeks**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	

		Missing	n (%)	n (%)	n (%)	
EQ-5D (Self care)	**6 weeks**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Usual activities)	**6 weeks**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Pain/discomfort)	**6 weeks**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Anxiety/depression)	**6 weeks**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	

		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
EQ-5D VAS	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	

Table 25: Patient satisfaction at follow-up (6 weeks and 6 months) summarised by treatment group

			ORIF	CCC	TOTAL	P-value
Injured ankle today compared to before injury	**6 weeks**	Very much worse	n (%)	n (%)	N	xx.xx
		Much worse	n (%)	n (%)	N	
		Minimally worse	n (%)	n (%)	N	
		No change	n (%)	n (%)	N	
		Minimally improved	n (%)	n (%)	N	
		Much improved	n (%)	n (%)	N	
		Very much improved	n (%)	n (%)	N	
		Missing	n (%)	n (%)	N	
	6 months	Very much worse	n (%)	n (%)	N	xx.xx
		Much worse	n (%)	n (%)	N	
		Minimally worse	n (%)	n (%)	N	
		No change	n (%)	n (%)	N	
		Minimally improved	n (%)	n (%)	N	
		Much improved	n (%)	n (%)	N	
		Very much improved	n (%)	n (%)	N	
		Missing	n (%)	n (%)	N	
Patient Satisfaction	**6 weeks**	Very dissatisfied	n (%)	n (%)	N	xx.xx
		Somewhat dissatisfied	n (%)	n (%)	N	
		Neither satisfied nor dissatisfied	n (%)	n (%)	N	
		Somewhat satisfied	n (%)	n (%)	N	
		Very satisfied	n (%)	n (%)	N	

		Missing	n (%)	n (%)	N	
	6 months	Very dissatisfied	n (%)	n (%)	N	xx.xx
		Somewhat dissatisfied	n (%)	n (%)	N	
		Neither satisfied nor dissatisfied	n (%)	n (%)	N	
		Somewhat satisfied	n (%)	n (%)	N	
		Very satisfied	n (%)	n (%)	N	
		Missing	n (%)	n (%)	N	

Table 26: Range of movement at follow-up (6 weeks and 6 months) summarised by treatment group

			ORIF	**CCC**	**TOTAL**	**P-value**
Angle of ankle dorsiflexion	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Angle of ankle plantarflexion	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx

		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Eversion as percentage of normal	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Inversion as percentage of normal	**6 weeks**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Started partial weight bearing	**6 weeks**	Yes	n (%)	n (%)	N	xx.xx
		No	n (%)	n (%)	N	
		Missing	n (%)	n (%)	N	

	6 months	Yes	n (%)	n (%)	N	xx.xx
		No	n (%)	n (%)	N	
		Missing	n (%)	n (%)	N	

Table 27: Timed 'Get up and go' walking test at 6 month follow-up summarised by treatment group

		ORIF	**CCC**	**TOTAL**	**P-value**
Timed 'Get up and Go' (seconds)	Mean	xx.xx	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx	
	Std. Deviation	xx.xx	xx.xx	xx.xx	
	Median	xx.xx	xx.xx	xx.xx	
	Minimum	xx.xx	xx.xx	xx.xx	
	Maximum	xx.xx	xx.xx	xx.xx	
	Missing	xx.xx	xx.xx	xx.xx	
Not completed in under 5 minutes	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	**N**	
	Missing	n (%)	n (%)	N	
Did patient use walking aid(s)	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	**N**	
	Missing	n (%)	n (%)	N	
Unable to complete test due to	Non-weight bearing	n (%)	n (%)	N	xx.xx
	Declined to complete test	n (%)	n (%)	**N**	
	Other physical limitation	n (%)	n (%)	N	
	Other	n (%)	n (%)	**N**	
	Missing	n (%)	n (%)	N	

Listing 18: If yes walking aid(s) used during test, please specify

Listing will be by treatment group. The following will be listed: patient number and the walking aid(s) that were used

Listing 19: Other reasons why patient unable to complete test

Listing will be by treatment group. The following will be listed: patient number and reason unable to complete test

Table 28: Process variables summarised by treatment group

			ORIF	CCC	TOTAL	P-value
Screening	Time from injury to screening	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Randomisation/Theatre	Time from randomisation to Theatre procedure	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Treatment	Time from injury to treatment	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	

		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Theatre	Time from entry into anaesthetic room to start time in theatre	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	Time from start to end of procedure in theatre	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Additional theatre procedure	Time from primary procedure to additional procedure in theatre	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	

	Time from entry into anaesthetic room to start time in theatre	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	Time from start to end of procedure in theatre	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Theatre/Hospital discharge	Time from theatre to hospital discharge	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Hospital discharge/Hospital readmission	Time from hospital discharge to readmission	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	

		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	