NETSCC, HTA

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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

Ethics Ref: 09/H0604/129

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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)

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 5 years - assessment of function and complications

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)	Radiological fracture and joint position measurement Time in and out of theatre, experience of operating surgeon, implants 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
Measures at 5 years (outpatient - 30 minutes)	This will be an optional clinical and radiological assessment: Timed 'Get up and Go' test Olerud & Molander Ankle Score Ankle range of movement Radiological fracture and joint position measurement
NB: The funding for this assessment is separate from the HTA application and not included in costings	

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), for assessment by two surgeons. The measurements will be undertaken independently, and any disagreement 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.

At 5 years, participants will be asked to attend the outpatient department for clinical and radiological examinations to assess functional outcome and any complications.

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)

5 years - 30 minutes

To be undertaken by member of research team

- Olerud & Molander Ankle Score - a patient reported functional outcome measure. 10 questions covering areas of physical ability
- Ankle range of movement - goniometer measurement of dorsiflexion, plantarflexion, inversion and eversion
- Radiological measurements of fracture and ankle joint congruence (x-rays to be sent to the Oxford Trials Unit for detailed measurement)
- Timed 'Get up and Go' test - to assess 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. (Some participants will be contacted at 5 years and invited to attend for a further follow up but this phase will be a separate sub study).

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 from Oxford for this trial has been used as a primary source to inform estimates of variance and treatment effects measured using the Olerud & Molander score (29), and a range of secondary outcomes. We have tested the sensitivity of these estimates against data available in the published literature.
Setting the parameters for the equivalence study is a challenge. We have set the maximal difference between treatments at 10% on the Olerud & Molander score (equating to a Cohen's effect size of less than 0.16); we believe this is not clinically significant, and is the amount patients would be prepared to trade in the effectiveness of a surgical treatment versus a non-surgical treatment. We have also elicited similar responses from orthopaedic surgeons in an informal survey. As part of the study we will undertake a valuation study to ensure these estimates are reasonable. We have utilised one-sided testing in the power calculation since we are not trying to prove that the new treatment is better than the standard, and we gain considerable statistical efficiency. Power will be set at 80% according to Food and Drug Administration (FDA) recommendations for bioequivalence studies. Utilising data from our pilot study and the published literature, we estimate the percentage success rate of the surgical group to be of the order of 65 to 70%. At the outset we will aim to recruit a total of 620 patients, based on a success rate of 65% in the control arm, a one-sided alpha ($p<0.05$), a power of 80% and a maximal difference to conclude equivalence of 10%. This is a pragmatic estimate and it includes a 10% loss to follow-up. The assumptions underlying the estimate will be reviewed at regular intervals, and modified

accordingly. Over time, the estimates would be expected to stabilise and should decrease in size with the probability that the trial will be smaller than we have anticipated. The target sample size is adequately powered to determine equivalence in the continuous scored outcomes, and allows for a range of possible eventualities

Sample size requirement in each of arm of the study under a range of success rates and alpha.

	Alpha (1 sided) 0.1	Alpha (1 sided) 0.05	Alpha (1 sided) 0.025
0.7	189	260	324
0.65	205	281	356

8.2 Analysis of Endpoints

In equivalence testing the relevant null hypothesis is that a difference of at least δ exists, and the trial is targeted at disproving this in favour of the alternative that no difference exists**.** This approach is indicated when the objective is to ensure that the new agent is not inferior to the standard. In an equivalence trial it is recommended to carry out a treatment received and intention to treat analysis, aiming to demonstrate equivalence in either case. With respect to other aspects of analysis, equivalence trials are similar in nature to comparative trials.

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

- that the confidence interval for the difference between the two treatments lies entirely within the equivalence range so that equivalence may be concluded with only a small probability of error
- that the confidence interval covers at least some points which lie outside the equivalence range, so that differences of potential clinical importance remain a real possibility and equivalence cannot safely be concluded
- that the confidence interval is wholly outside the equivalence range (though this is likely to be rare)

An analysis of all participants who complete the trial will be undertaken and 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. Our main analytical methods will be generalised linear models, and all analyses will be adjusted for important baseline co-variates to maximise precision. A data analysis plan will be agreed with the Data Management and Ethics Committee (DMEC).

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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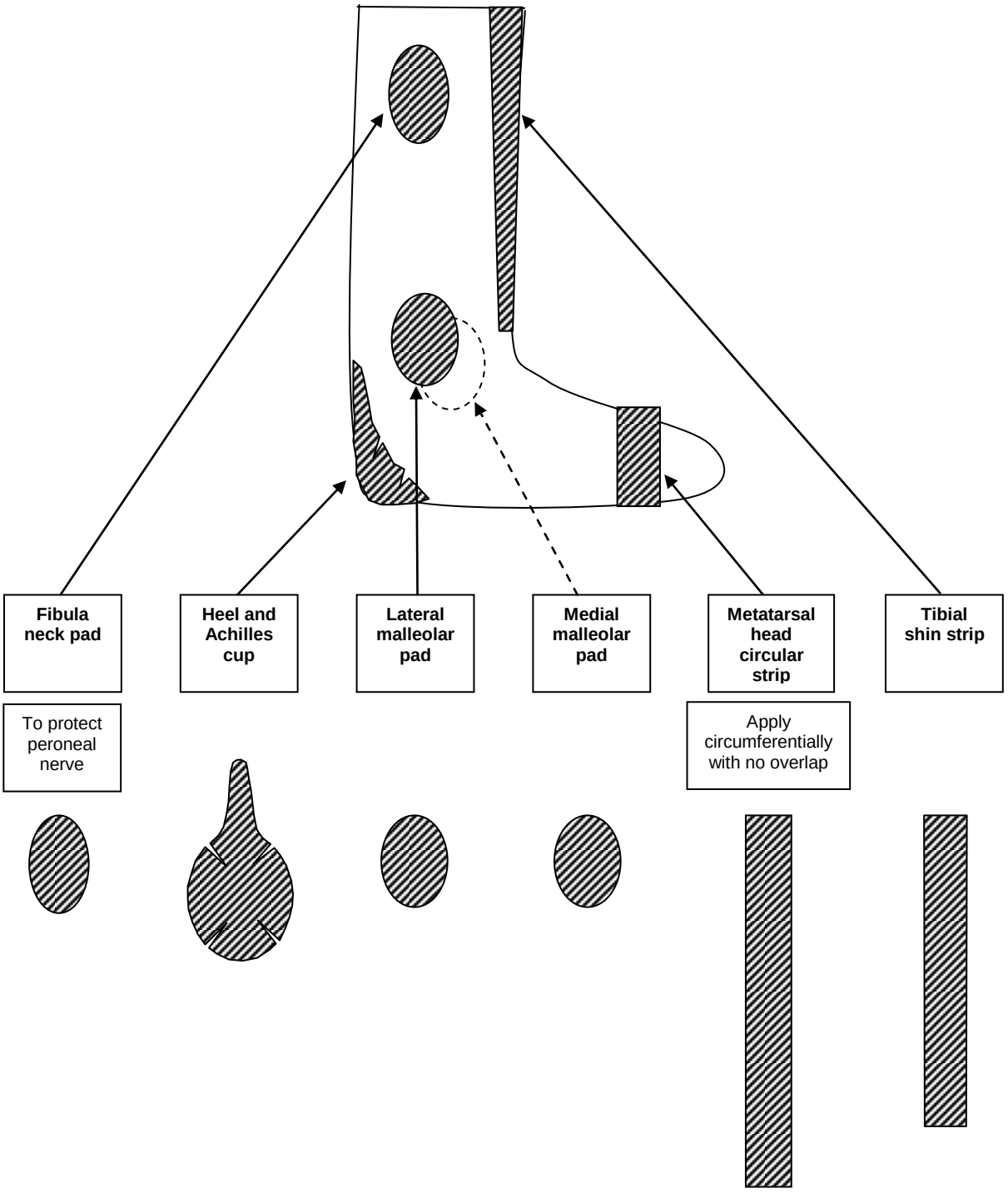
14. APPENDICES

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	*5 years*
• 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	• *X-ray* • *Clinical examination*