ART: **A**nkle **R**ecovery **T**rial

Does early mobilisation after **A**nkle fracture surgery enhance **R**ecovery? A randomised controlled **T**rial comparing the use of plaster versus removable support boot.

Protocol Version and date	Version 1.6 – 05/03/2018
ISRCTN	15497399
REC Reference	14/SC/1409
Funder:	NIHR Research for Patient Benefit (RfPB)
Sponsor:	Poole Hospital NHS Foundation Trust
Sponsor Reference Number:	P140218

General Information

This document describes the ART trial and provides information about procedures for entering patients into the trial. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the study coordinating site to confirm they have the most up to date version. The protocol has been developed with reference to the Poole Hospital NHS Foundation Trust protocol template.

Lead applicant and Co-applicants

Chief Investigator:	Mr Bob Sangar Poole Hospital NHS Foundation Trust
Consultant Surgeon:	Mr Mark Farrar Poole Hospital NHS Foundation Trust
Trial Statistician:	Professor Peter Thomas, Bournemouth University Clinical Research Unit
Methodologist:	Dr Sharon Docherty Bournemouth University Clinical Research Unit
Qualitative Researcher:	Helen Allen Bournemouth University Clinical Research Unit
Health Economist:	Dr Elsa Marques University of Bristol
Senior Trial Manager:	Christopher Hayward Plymouth University Peninsula Clinical Trials Unit
Lead Physiotherapist:	Rachel Martin Poole Hospital NHS Foundation Trust

Operational research team contact details

Chief Investigator:	**Mr Bob Sangar** Poole Hospital NHS Trust Longfleet Rd, Poole, Dorset BH15 2JB Tel: 01202 665511 anuraag.sangar@poole.nhs.uk	**Trial Manager: (General Enquires)**	**Lee Tbaily** Poole Hospital NHS Trust Research & Innovation Room 38, Cornelia House Longfleet Rd, Poole, Dorset, BH15 2JB Tel: 01202 442025 Lee.Tbaily@poole.nhs.uk
Senior Trial Manager:	**Christopher Hayward** Peninsula Clinical Trials Unit Rm N16, ITTC Building 1 Tamar Science Park Derriford, Plymouth PL6 8BX Tel: 01752 431020 Christopher.Hayward-4@plymouth.ac.uk	**Data Manager:**	**Paul Williams** Peninsula Clinical Trials Unit Rm N16, ITTC Building 1 Tamar Science Park Derriford, Plymouth PL6 8BX Tel: 01752 439828 Fax: 01752 315254 Paul.Williams@plymouth.ac.uk
Sponsor:	**Sarah Chessell** Poole Hospital NHS Trust Research & Innovation Cornelia House Longfleet Rd, Poole, Dorset Tel: 01202 448125 Sarah.chessell@poole.nhs.uk	**Lead site Research Physiotherapists:**	**Rachel Martin & Adrian Hand** Poole Hospital NHS Trust Physiotherapy Longfleet Rd, Poole, Dorset, BH15 2JB Tel: 01202 448179 / 01202 442121 Rachel.martin@poole.nhs.uk Adrian.Hand@Poole.nhs.uk

Table of Contents

1. STUDY SYNOPSIS 6

2. ABBREVIATIONS 8

3. INTRODUCTION 9

4. AIMS AND OBJECTIVES 11

4.1. Aim 11

4.2. Objectives 11

4.2.1. Primary objective 11

4.2.2. Secondary objectives 11

5. STUDY DESIGN 11

5.1. Study design overview 11

5.2. Design and bias considerations 13

5.3. Duration of patient participation 13

6. SETTING 13

7. OUTCOME MEASURES 13

7.1. Primary Outcome measure 13

7.2. Secondary outcome measures 14

7.2.1. Functional data 14

7.2.2. Healing status 14

7.2.3. EQ-5D-5L 14

7.2.4. Complications 14

7.2.5. Return to usual activities 15

7.3. Baseline Characteristics 15

7.3.1. Demographics and socioeconomics 15

7.3.2. Fracture characteristics 15

7.4. Resource Use 15

7.5. Adverse events 16

7.6. Patients' experiences 16

7.7. Mobilisation and adherence to exercise 16

8. PARTICIPANT SELECTION 17

8.1. Inclusion Criteria 17

8.2. Exclusion Criteria 17

8.2.1. Justification of exclusion criteria 17

8.3. Withdrawal criteria 17

9. STUDY SCHEDULE 18

9.1. Pre-trial patient management 19

9.2. Patient identification and approach *19*

9.3. Baseline clinic visit (2 weeks post-surgery) *19*
9.3.1. Consent process 19
9.3.2. Baseline questionnaire completion 20
9.3.3. Baseline CRF completion 20
9.3.4. Randomisation 20
9.3.5. Provision of treatment 21
9.3.6. Provision of Patient Diary 21
9.3.7. End of baseline visit procedures 21

9.4. 4-week follow-up visit (6 weeks post-surgery) *22*
9.4.1. 4-week follow-up questionnaire completion 22
9.4.2. 4-week follow-up CRF completion 22
9.4.1. Provision of Patient Diary 23
9.4.2. End of 4-week follow up visit procedures 23

9.5. 5-week follow-up questionnaire completion *23*

9.6. 10-week follow-up (12 weeks post-surgery) *24*
9.6.1. 10-week follow-up questionnaire completion 24
9.6.2. 10-week follow-up CRF completion 24

9.7. Telephone interviews *25*

9.8. Radiographic Evaluation *25*

10. INTERVENTION DETAILS 25

10.1. Removable support boot *25*

10.2. Plaster Cast *26*

10.3. Associated Risks *26*

11. ASSESSMENT OF SAFETY 26

11.1. Standard definitions *26*

11.2. Reportable events *27*

11.3. Procedures for Serious Adverse Event reporting *27*
11.3.1. Assessment of severity and causality 27
11.3.2. Assessment of expectedness 29

11.4. Processing Serious Adverse Event report forms *29*
11.4.1. Onward reporting 29

12. STATISTICS AND DATA ANALYSIS 30

12.1. Sample Size Calculation *30*

12.2. Description of statistical methods *30*
12.2.1. Baseline descriptives: 30
12.2.2. Primary outcome: 31
12.2.3. Secondary outcomes: 32

12.3. Qualitative Component *33*

12.4. Economic Evaluation *33*

13. ETHICAL, REGULATORY, ADMINISTRATIVE AND QUALITY ASSURANCE 35

13.1. Ethical considerations *35*

13.2. Declaration of Helsinki *36*

13.3. Research Governance *36*
13.4. Study Management *36*
13.5. Trial Steering Committee *36*
13.6. Monitoring *37*
13.7. Audit and Inspection *37*

14. DATA HANDLING AND RECORD KEEPING **37**
14.1. Participant Numbering *37*
14.2. Source data *37*
14.3. Data Entry *37*
14.4. Data confidentiality and security *37*
14.5. Archiving *38*

15. FINANCE, INDEMNITY AND INSURANCE **38**
15.1. Funding *38*
15.2. Sponsor *38*
15.3. Indemnity *38*

16. PUBLICATION POLICY AND INTELLECTUAL PROPERTY **38**
16.1. Publication Policy *38*
16.2. Intellectual Property *38*

17. REFERENCES **39**

Figure 1 Study design flowchart 12

Table 1: Tabulated Study Schedule 18
Table 2: Definitions of Causality 29

1. STUDY SYNOPSIS

Study title	Does early mobilisation after **A**nkle fracture surgery enhance **R**ecovery? A pragmatic multi-centre randomised controlled **T**rial with qualitative component and health economic analysis comparing the use of plaster versus removable support boot **(ART)**.
Short study title:	The Ankle Fracture Recovery Trial **(ART)**
Study design	This study is designed as a pragmatic multi-centre randomised controlled trial with qualitative component and health economic evaluation comparing plaster cast and support boots as methods of post-operative ankle fracture management.
Study participants	***Inclusion Criteria*** • Received surgery for fixation of unstable ankle fracture • Provision of informed consent to participate ***Exclusion criteria*** • Under 16 year olds (skeletally immature). • Poor skin condition at operation site. • Serious concomitant disease (e.g. stroke, osteoporosis, arthritis). • Diabetic neuropathy/other sensory neuropathy (lack of sensation). • Non-ambulatory prior to injury. • Active leg ulceration. • Patients who are unable to understand the study information or unable to complete the outcome questionnaires. • Surgeon concerned about quality of fixation/integrity of wound. • Fracture requiring further stabilisation in/around the ankle (e.g. syndesmosis). • Open ankle fracture (bone broken through skin). • Participant is a participant in other concurrent interventional research which may over-burden the participant or confound data collection. • Concomitant injuries which will have a confounding effect on rehabilitation in the opinion of the investigator.
Number of participants	276 patients in total (138 in each treatment group).
Follow-up duration	Patients will be followed up in clinic at 4 weeks post-baseline (6 weeks post-operatively) and via questionnaires), at 5 weeks post-baseline (7 weeks post-operatively) and 10 weeks post-baseline (12 weeks post-operatively). Qualitative telephone interviews with up to 20 participants will take place after the 10-week follow up.

Planned study period	48 months (37 month recruitment period)
Study aim	To evaluate the relative effectiveness and cost-effectiveness of two methods of post-operative ankle fracture management (plaster versus removable support boot allowing range of movement) and to provide evidence-based recommendations for best care in clinical practice.
Study objectives	1. To determine whether there is a difference in ankle function between the two types of treatment. 2. To determine whether there is a difference in quality of life between the two treatments. 3. To estimate which is the cost-effective treatment option to inform decision-making. 4. To explore patient experiences and the psychological and social impact of their treatment.
Outcome measure data	**Primary outcome:** The primary outcome measure for this study is the Olerud and Molander ankle score at five weeks after randomisation. **Secondary outcomes:** • Ankle functional data (range of movement, weight-bearing) • Standardised measure of general quality of life (EQ-5D-5L) • Healing status • Complications • Return to Usual Activities **Other data collected;** • Baseline characteristics • Healthcare resource use • Adverse events • Mobilisation and adherence to exercise
Qualitative component	Telephone interviews conducted at around the 10 week follow up time point with up to 20 participants to address: • Experiences of each type of treatment (plaster/boot). • Lifestyle implications – individual (e.g. washing), family, social, psychological, work, financial, residential, diet, transport (e.g. driving), leisure activities, and independence. • Expectations, mind-set, confidence, including the perceived views of carers where appropriate.
Interventions	Patients will be allocated in a 1:1 ratio with both groups weight-bearing as tolerated: 1. **Plaster below knee** i.e. immobilised for four weeks. 2. **Removable support boot** with range of movement for four weeks.

2. **ABBREVIATIONS**

AE	Adverse Events
BUCRU	Bournemouth University Clinical Research Unit
CI	Chief Investigator
CEAC	Cost Effectiveness Acceptability Curves
CRF	Case Report Form
DVT	Deep Vein Thrombosis
HE	Health Economist
ICER	Incremental Cost Effectiveness Ratio
ICH GCP	International Conference on Harmonisation, Good Clinical Practice
IEP	Image Exchange Portal
INMB	Incremental Net Monetary Benefit
ISRCTN	International Standard Randomised Clinical Trial Number
NIHR	National Institute for Health Research
OMAS	Olerud and Molander Ankle Score
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PSS	Prescribed Specialised Services
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SAE	Serious Adverse Events
TMG	Trial Management Group
TSC	Trial Steering Committee
WPAI	Work Productivity and Activity Impairment Questionnaire

3. **INTRODUCTION**

Approximately two million ankle fractures occur annually in the United Kingdom affecting 3.6% of the population, 75% in under 60 year olds[1], of which a high proportion need surgical fixation, with considerable cost to the National Health Service. Indeed, 7.2% of all fractures admitted to Poole Hospital are ankle fractures and 197 underwent surgical fixation in 2011[2] illustrating the scale of the issue (audit data suggest 104 in Basingstoke in 2012 and 76-80 in six month periods in 2009 and 2010 respectively in Portsmouth). Ankle fractures are a cause of short-term and sometimes long-term disability and pain. These injuries frequently require many weeks off work with subsequent economic consequences[3]. Six weeks of immobilisation in plaster is frequently advocated for all ankle fractures *not* requiring surgery. It is also recognised practice to immobilise a broken ankle after surgery for comfort, support and to allow the wound to heal. This tends to be with a plaster because it is cheap and readily available in the operating theatre and has been used for decades.

However, there has been no consensus for the management of ankle fractures post-operatively for those ankle fractures that need surgical fixation. Therefore, current treatment is not standardised in many Trusts in the National Health Service. There is evidence to suggest that removing plasters and wearing removable boots that allow early weight-bearing and range of movement of the ankle, maximises rehabilitation potential.

A number of studies have investigated the benefits of early weight-bearing and mobilisation following ankle fracture fixation. Early return to function should be the principal goal following surgical management[3]. Traditionally, patients have been managed in a plaster cast and have been strictly non-weight-bearing (hopping on their unaffected leg).

However, immobilisation can result in reduced range of movement and muscle deterioration[4-6]. Early mobilisation of ankles following open reduction and surgical internal fixation provides short-term benefits in improved range of movement, reduced swelling, pain, an earlier return to work, improved patient satisfaction, and better ankle function[7].

At Poole Hospital, fitting patients with a plaster following open reduction and surgical internal fixation costs approximately £20.84 for materials plus plaster technician labour costs for 10-15 minutes per case. Although there are a range of boots available on the market at varying prices, those used are chosen for their quality and value for money – for example, the pneumatic walker boot currently in use at Poole Hospital costs £52.39 and we expect it may be equally labour intensive (information provided by plaster technicians).

However, the boot may be more comfortable as it can be removed at night and for washing, and ultimately improves patient satisfaction[8]. Despite boots having fewer limitations than plaster, they can still be considered cumbersome and disposal of plasters and boots both have environmental impact.

Furthermore, some studies report conflicting and inconclusive findings with regards to complications. Lehtonen et al[9] found wound infections in 6.6% of those who mobilised early and a high incidence of deep vein thrombosis. On the other hand, Vioreanu et al[6] found patients who exercised once primary wound healing had taken place had fewer wound infections and the immobilised group had problems with deep vein thrombosis. Farsetti et al[10] compared two case series of 22 patients and found no correlation between wound complications and continuous passive movement applied for the first three weeks post-operatively.

Although there are two current trials underway, one in London[11], the other in Toronto[12], the London study is a smaller study (n=76) and does not encourage active movement through range of movement exercises whilst the Toronto study is unrealistic not allowing weight-bearing in plaster. The most recent systematic review by Thomas et al[3 (p 674)] and a Cochrane report by Lin et al[13 (p 431)], both recommend the need for more research with well-designed and conducted trials with adequate numbers and reporting. There is limited evidence supporting the use of a removable type of immobilisation and active range of movement and no previous studies, to the research team's knowledge, have investigated the socio-economic factors and psychological impact which may be related to return to function, independence, and work.

This research is needed now to ensure that the post-operative management of patients who have sustained an ankle fracture is consistent with best practice and considerate of patient experience. The research is particularly timely in this economic climate to allow patients to optimise their rehabilitation potential and return to full function and normal employment as soon as possible. There is currently no definitive study advising on the optimal treatment and rehabilitation of ankle fractures following surgery. This randomised study aims to objectively provide an answer. In particular, the study will provide guidance on which form of post-surgical treatment is more reliably able to restore an individual's independence, function, and mobility after ankle fracture surgery; as well as the probability of being a cost-effective treatment option for the NHS. It will also investigate whether the treatment regime influences a patient's return to work as well as exploring the wider socio-economic implications of the two treatments.

As part of patient and public involvement for the design of this study, twelve telephone consultations were conducted with service users who had received treatment for ankle fractures. One of the most important issues to patients suffering from ankle fractures was the lack of hygiene when immobilised in a plaster. The advantage provided by a removable boot in terms of being able to visualise and mobilise tissues and joints has been alluded to in several studies.

If there is a clear advantage of one treatment over another in terms of outcomes and costs, then treatment can be standardised with recommendations being made for local and national policy guidelines. This will directly benefit patients, employers, healthcare providers and the wider economy.

4. AIMS AND OBJECTIVES

4.1. Aim

To evaluate the relative effectiveness and cost-effectiveness of two methods of post-operative ankle fracture management (plaster versus removable support boot with range of movement) and to provide evidence-based recommendations for best care in clinical practice.

4.2. Objectives

4.2.1. Primary objective

- To determine whether there is a difference in function between the two types of treatment.

4.2.2. Secondary objectives

- To determine whether there is a difference in quality of life between the two treatments.
- To determine whether there is a difference in healing, complications and adverse events between the two treatments.
- To determine whether there is a difference between return to work, driving and usual activities between the two treatments
- To determine which is the most cost-effective treatment option if provided in the NHS.
- To explore patient experiences and the psychological and social impact of their treatment.

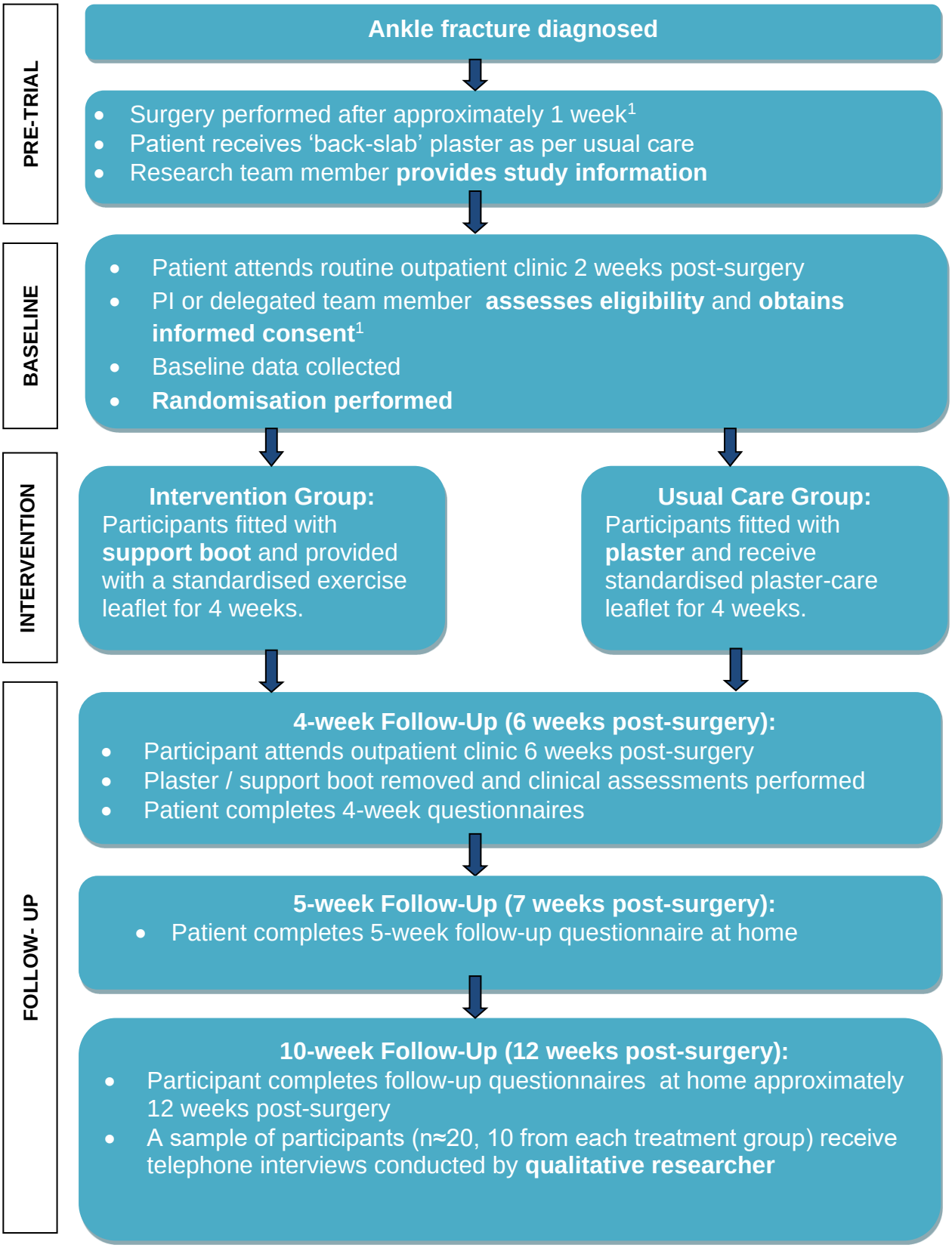
5. STUDY DESIGN

5.1. Study design overview

This study is designed as a pragmatic multi-centre randomised controlled trial with qualitative component and health economic evaluation comparing plaster cast and removable support boots as methods of post-operative ankle fracture management.

Figure 1 Study design flowchart

Illustrating flow of patients through the trial and the time points for data collection.



[1] Patients not requiring surgery, or who are ineligible or unwilling to participate in the trial will be excluded from the trial and managed as per usual care.

5.2. Design and bias considerations

The nature of the two interventions clearly makes it impossible to blind the patient or treating clinicians. Moreover the appearance of the leg at the follow-up appointments will make the allocation evident, so that those involved in outcome assessment also cannot be blinded. However, the trial statistician and data analysts will remain blinded to group allocation until the analyses are completed. Furthermore, the radiographic evaluations of healing status performed by the Chief Investigator at the end of the study (see section 9.8 Radiographic Evaluation) will be performed in a blinded manner.

5.3. Duration of patient participation

The expected duration of patient participation is approximately 10 weeks starting from randomisation and collection of baseline measures at the first clinic visit. Up to twenty participants will be selected for qualitative interviews soon after the 10-week time point. End of patient participation will be defined as the completion of data collection for the last patient followed-up in the study.

6. SETTING

The study will be conducted at three investigator sites initially; Poole Hospital NHS Foundation Trust, Basingstoke and North Hampshire NHS Foundation Trust and Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust. Other sites may be invited to participate in the event that recruitment rate is lower than anticipated, subject to REC and NHS approvals. Conduct of the trial at each site will be led by a local Principal Investigator with support from research personnel trained in good clinical practice. Support will also be required from a physiotherapist(s) to perform protocol-specific clinical assessments, for which training will be provided.

7. OUTCOME MEASURES

This section is intended to list, describe and justify choice of outcomes rather than to describe how the data are collected for research purposes. Data collection is addressed in Section 9.

7.1. Primary Outcome measure

The primary outcome measure for this study is the Olerud and Molander[14] ankle symptom scale at five weeks after randomisation. The five week post-baseline data collection period is the critical period, as this is when it is anticipated that the group who had boots will have a greater level of function[3,6]. Most patients in both groups will no longer be using their allocated treatment and will have had at least 3 days without a plaster cast or boot to enable functional recovery of the ankle to be assessed. The study will also compare the ten week Olerud and Molander[14] ankle score to check whether any differences between groups still remain, and to see whether the ten week measures have returned to their (estimated) pre-injury values.

7.2. **Secondary outcome measures**

7.2.1. Functional data

Functional data including range of movement (dorsiflexion, plantarflexion, inversion, eversion (degree angles)), circumferential swelling and weight-bearing status at four weeks post baseline. Range of motion will be assessed using a goniometer. Weight-bearing will be classified as touch weight-bearing, partial weight-bearing or full weight-bearing. Circumferential swelling of the injured ankle will be measured using a tape measure. Circumference of the non-injured ankle will be measured in the same way and used as a comparison. Range of movement assessments and circumferential measurements must be conducted by a physiotherapist trained in the requirements of the study protocol and recorded in the patient's medical record.

7.2.2. Healing status

Healing status will be determined by the Chief Investigator's blinded review of pre-operative, intra-operative and post-operative X-ray films at the end of the study (see section 9.7 Radiographic Evaluation). The review will evaluate integrity of the surgical metal work (displaced / undisplaced) and whether or not there is evidence of fracture healing at the 4 week time point.

7.2.3. EQ-5D-5L

EQ-5D-5L will be completed by participants at baseline, 4-week, 5 week and 10-week time points. There is likely to be a marked difference in quality of life once the boot/ plaster is removed, and so measurements will be made at both 4 weeks (with the boot/ plaster on) and 5 weeks (with the boot/ plaster usually off). We anticipate that measurement at 4 weeks will attribute to the restrictive nature of the boot/ plaster, whilst at 5 weeks will collect data on recovery/ healing. The EQ-5D-5L is a standardised descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. It captures relevant issues e.g. walking, problems washing/dressing, as well as problems with usual activities including work and family/leisure activities, pain, and psychological impact[15]. It will be used to derive quality adjusted life years (QALYs).

7.2.4. Complications

Complications including; Blisters (presence and severity; minor/major), Pressure sores (presence and severity; grade 1-5), Failure of fixation (presence; medial/lateral/both), Operation/revision surgery, Wound breakdown, Wound infection (presence and severity; Minor (treatable with antibiotics/dressing) / major (needs surgical debridement), Compartment Syndrome, DVT (presence; below knee/above knee), Nerve Injury (presence; sensory/motor/both) and Pulmonary embolism occurring up to 12 weeks post-surgery will be recorded. Complications recorded will include those reported by patients, identified by the PI or delegated member of the research team during their routine clinical assessment and from their review of hospital records.

7.2.5. Return to usual activities

At baseline, patients will be asked for their employment status prior to injury (unemployed, homemaker, volunteer, full time education, part-time paid employment, full time paid employment). At 10 weeks participants will be asked for their current employment status and will be asked whether their ankle injury has an impact on every day activities (0 to 10 scale anchored by no effect on daily activities and completely prevented daily activities).

Absenteeism (days off work), presenteeism (feeling less productive at work), and time off usual social activities, are productivity losses that we will measure at 4 and 10 weeks, by questions included in the resource use questionnaire. Participants will also be asked if they drove pre-injury, whether they had started driving again, and the date they resumed driving.

7.3. **Baseline Characteristics**

7.3.1. Demographics and socioeconomics

Gender, age, marital status living situation, education level, employment status, driving status and pre-surgery height and weight/BMI will be collected at baseline.

7.3.2. Fracture characteristics

Characteristics of the fracture (classification, pattern) and a description of the hardware used during surgery will be recorded following a blinded review of radiographs performed by the Chief Investigator (see section 9.7 Radiographic Evaluation). Classification will be coded as Weber A, B or C, pattern will be coded as medial malleolar fracture or deltoid ligament injury .Fracture Complexity will be reported in the baseline CRF and will be coded as simple fibular fracture and comminuted fracture.

7.4. **Resource Use**

(i) Resources associated with administration of treatment in both arms (including materials used and time and grade of staff involved in fitting/removing the plaster/boot and providing the necessary instruction to patients) will be captured by the research team in the CRF at the 2 week post-surgery (baseline) and 6-week post-surgery (4 week post-randomisation) appointment in clinic.

(ii) Resources delivered by the treating hospital[1] at 10 weeks from randomisation will be collected from a review of patients' hospital notes at the end of the patient's participation. Data on inpatient admissions, outpatient appointments and outpatient therapies provided, as well as diagnostic tests performed will be collected onto CRF's by the research team from randomisation (2-week post-surgery) until last follow-up (12 weeks post-surgery). Date of event will be collected, to allow for costing the two different periods of resource use, in the two economic analyses.

[1] In this context, 'treating hospital' refers to the hospital in which the ankle fracture surgery is performed.

(iii) Participants' use of other health and social care resources, as well as informal care and loss of productivity, will be captured at the 4-week and 10-week time points via patient-completed questionnaires. Patient reported data will be collected from randomisation on:

(a) Community-based health care services used. This will include contacts with GP doctor and nurses at the GP practice, at home or by telephone, and other health services required such as community physiotherapist and occupational therapist visits Use of concomitant medications will also be patient reported.
(b) Secondary care visits to hospitals
(c) Use of social services, such as home help, food at home services and contacts with social worker.
(d) Productivity losses, including a measurement of absenteeism and presenteeism, by adapting a few questions from the Work Productivity and Activity Impairment Questionnaire (WPAI): General Health Version 2.0[16], a licence-free, well-known and validated questionnaire commonly used to measure productivity losses when patients take time-off work or are unproductive at work[17-18.] We will also collect losses in leisure time and informal care from friends and relatives.
(e) Private expenses, such as travel, privately paid therapies or lost income.

The primary outcome is collected at 5 weeks post randomisation. Collection of resource use should follow the same time frame, so that costs and outcomes can be compared within the period. However, we feel strongly that the first resource use questionnaire should be administered face-to-face in clinic at 4 weeks, and not at the 5 week data collection point. A first resource use questionnaire administered in clinic will allow patients to interface with the research team to clarify any queries; check the questionnaire for missing data; and instruct patients on how to complete the second questionnaire at home at 10 weeks. Patients' lives (and their resource use) will be very different after their cast or boot is removed at the 4 week visit and this may affect their recollection of health care needs. In addition, including resource use questions at the 5 week time point (3-10 days post 4 week appointment), would increase patient burden and jeopardize completeness of the primary clinical outcome. We will later approximate, using statistical methods, cost assumptions for 3-10 day incremental cost period.

7.5. **Adverse events**

Serious adverse events will be collected from the point of randomisation at each data collection time point for the duration of the study. See section 11 (Assessment of safety) for details.

7.6. **Patients' experiences**

Patients' experiences of their treatment will be explored via telephone interviews conducted by the qualitative researcher in the team. See section 12.3 (Qualitative component) for details.

7.7. **Mobilisation and adherence to exercise**

Data will be collected to assess whether participants have adhered to instructions to complete exercises. Physiotherapists will make recommendations for participants to exercise and mobilise their ankle as often in a day as pain allows based on an

advice leaflet specific to their treatment allocation (recommended at least 3 times a day.) Compliance will be defined as once per day or more.

8. PARTICIPANT SELECTION

8.1. Inclusion Criteria

Patients must satisfy the following criteria to be enrolled in the study:

- Received surgery for fixation of unstable ankle fracture
- Provision of informed consent to participate.

8.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study participation:

- Under 16 years old (skeletally immature).
- Poor skin condition at operation site.
- Serious concomitant disease (e.g. stroke, osteoporosis, arthritis).
- Diabetic neuropathy/other sensory neuropathy (lack of sensation).
- Non-ambulatory prior to injury.
- Active leg ulceration.
- Patients who are unable to understand the study information or unable to complete the outcome questionnaires.
- Surgeon concerned about quality of fixation/integrity of wound.
- Fracture requiring further stabilisation in/around the ankle (e.g. syndesmosis).
- Open ankle fracture (bone broken through skin).
- Participant is a participant in other concurrent interventional research which may over-burden the participant or confound data collection.
- Concomitant injuries which will have a confounding effect on rehabilitation in the opinion of the investigator.

8.2.1. Justification of exclusion criteria

Patients with serious concomitant diseases or concomitant injury are excluded because they may have different treatment and rehabilitation options. Patients with sensory neuropathy are excluded as they may be prone to developing pressure ulcers caused by poorly-fitting plaster casts/boots. Patients who have suffered an open ankle fracture are excluded because they are at greater risk of developing infection.

8.3. Withdrawal criteria

Participants have the right to withdraw their participation in the study at any time without affecting the standard of care the patient receives. Clinicians may also advise patients to withdraw from the study should they acquire significant concomitant disease during the course of this treatment. Once withdrawn, the patient will be advised to discuss their further care plan with their consultant. Withdrawal will not adversely affect patients' care in any way.

9. **STUDY SCHEDULE**

This section describes conduct of the study in chronological order, detailing procedures for data collection at each of the time points.

Table 1: Tabulated Study Schedule
A tabulated study schedule to illustrate all data collection at each time point of the study;

TIMEPOINT	Week -2 (Surgery)	Baseline[1] (+2 weeks)	Week 4[1] (+6 weeks)	Week 5[2] (+7 weeks)	Week 10[2] (+12 weeks)	End of Study
PRE-TRIAL:						
Surgery	X					
Patient Information	X					
ENROLMENT:						
Eligibility screen		X				
Informed consent		X				
Baseline fracture characteristics		X				X[3]
Baseline socio-demographics		X				
Randomisation		X				
INTERVENTIONS:						
Plaster Cast		●	●			
Removable Support Boot		●	●			
Time to fit / remove Intervention		X	X			
ASSESSMENTS:						
Olerud & Molander Questionnaire		X		X	X	
EQ-5D-5L Questionnaire		X	X	X	X	
Resource Use[4]			X		X	
Return to usual activities					X	
Range of Ankle Movement			X			
Weight Bearing Status			X			
Circumferential Swelling			X			
Complications			X		X	
Serious Adverse Events		●	●	●	●	
Healing Status						X[3]
Participant Interviews					X	

[1] Baseline and 4-week follow-up data collected during participants' clinic visits
[2] 5-week and 10-week follow-up data completed by participants at home (sections 9.5 and 9.6)
[3] Healing status, fracture classification and pattern will be obtained by CI's blinded review of X-rays at end of study
[4] Resource use data collected primarily by patient-completed questionnaire. Services delivered by the treating hospital will be obtained by research teams' review of hospital records

9.1. Pre-trial patient management

Patients will undergo surgical fixation in accordance with local policy and practice. After surgery and prior to discharge, patients will be fitted with a 'back slab' plaster; a plaster support which temporarily immobilises the broken ankle and which has an incomplete front section so as to accommodate swelling. Prophylactic anticoagulation therapy (minimising risk of developing a blood clot) will be given as appropriate. This post-operative management will be provided in accordance with local policy and practice before the patient is discharged from hospital.

9.2. Patient identification and approach

Surgeons at participating sites will be made aware of the study and the profile of potentially eligible patients by the PI. Potentially eligible patients will be approached by a member of the local research team (employees of the Hospital Trust, usually research physiotherapists or research nurses) to discuss the ART trial - preferably prior to being discharged from hospital following their ankle surgery. In the event that the patient is discharged before they can be approached, a member of the research team may contact the patient at home. The research team member will briefly describe the trial and will provide the patient with a Participant Information Sheet (PIS). Patients will be advised that they will be invited to take part in the trial when they attend their routine post-operative outpatient visit, and that they may contact a member of the research team in the meantime with any queries (contact details given in the PIS). Between receiving the PIS and attending their routine post-operative outpatient visit, patients will have up to 2 weeks to consider participating in the trial but importantly, they must have no less than 24 hours. A record of the number of patients undergoing surgical fixation for unstable ankle fracture and those approached will be maintained by the research team at each site.

9.3. Baseline clinic visit (2 weeks post-surgery)

9.3.1. Consent process

At the routine post-operative outpatient visit, typically around two weeks after surgery, patients will be approached by the PI or delegated member of the research team in order to discuss participation in the trial. Potentially eligible patients who express willingness to participate will be asked to provide consent in accordance with Good Clinical Practice. The consent process will involve a full explanation of the trial given by the person taking consent. The person responsible for taking consent will be trained in GCP and Informed Consent. Patients will be advised that they are under no obligation to take part and that their ongoing care will be unaffected if they choose not to take part. Patients who choose not to take part will be asked to provide a reason for declining, but will be told that they do not have to give a reason if they wish not to. Patients will also be advised that they are free to withdraw from the trial at any time and that doing so will not affect their ongoing care.

Following this discussion, patients who are willing to participate will be asked to complete, sign and date the trial consent form, which will also be signed and dated by the person obtaining consent.

Eligibility will be determined via clinical assessment, patient questioning and review of the patients' hospital notes. The PI is responsible for confirming eligibility and for

obtaining consent but may delegate these duties appropriately to other members of the research team. Such delegation will be captured on a site-specific site delegation log. Any person obtaining written informed consent must have current GCP training and have received trial-specific training from the trial team. No clinical trial procedures will be conducted prior to taking consent from the participant.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy placed in the patient's hospital notes. Note that any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee. If necessary, this information will be communicated to all participants and they will be asked to re-confirm consent in light of the new information.

Patients who are found to be ineligible or who are unwilling to participate will be managed as per usual care. Reasons for non-participation (where given) will be recorded by the research team at each site.

9.3.2. Baseline questionnaire completion

After eligibility has been confirmed and written consent obtained, and prior to randomisation, patients will be provided with a questionnaire booklet to be completed during the visit. The baseline questionnaire booklet will comprise the following questions;

- Demographic and socio-economic questions
- Pre-injury Olerud and Molander (1984) ankle score (see section 7.1)
- EQ-5D-5L (see section 7.2)

9.3.3. Baseline CRF completion

A member of the research team will transcribe the following information from the patient's hospital record into the trial case report form (CRF):

- Participant information; name, date of birth, address contact details and preferred method of contact (to facilitate sending and retrieval of questionnaires and reminder alerts.)
- Fracture information; date of fracture, date of surgery, fracture side, complexity (Simple or comminuted fracture.)
- Weight and Height to compute Body Mass Index (BMI); participants may be weighed and measured at this visit if a recent weight and height is not available in the hospital notes.

9.3.4. Randomisation

Following completion of baseline information collection, a member of the research team will randomise the participant to one of the two treatment groups; Removable support boot, or plaster.

Patients will be randomised in order to minimise systematic bias, using a secure web-based system designed and maintained by the Peninsula Clinical Trials Unit

(PenCTU) according to the Unit's standard operating procedures. Computer generated randomisation codes prepared by the PenCTU will be kept secure, with access restricted to the data management team at the PenCTU. Participants will be allocated to the support boot group (intervention) or to the plaster group (control) in a 1:1 ratio, using random, even, block sizes between 2 and 8 to generate the allocation sequence and achieve balance in the numbers of participants allocated to each group. Randomisation will be stratified by site. The web-based randomisation system will be accessed securely via unique log-in details provided to each local team member by the CTU. The system ensures that allocation is appropriately concealed until the point of randomisation.

Upon randomisation, each participant will be assigned a unique Trial Number which will be used as the principal identifier on trial data collection forms and questionnaires. The research team member will disclose the allocation to the participant and will ensure the allocation is followed as described below.

9.3.5. Provision of treatment

Following allocation to treatment group, the patient will be directed to the facility (e.g. plaster room) in order to receive treatment. The support boot/below knee plaster (as per allocation) will be fitted by the plaster room technicians in accordance with local practice once any clips/stitches are removed. The time taken and materials used by plaster room technicians in fitting the boot/plaster in each case will be recorded on a designated form by the research team. A physiotherapist trained in the requirements of the study protocol will provide the patient with an advice leaflet specific to the participant's treatment allocation and teach them the exercises detailed. A member of the research team will also record the time the physiotherapist spends on educating patients about their treatment and the associated leaflets. These data will be used to cost the delivery of treatment in both arms for the economic evaluation as described in section 12.4.

9.3.6. Provision of Patient Diary

Completion of follow-up questionnaires may be difficult for some patients. Missing data and recall bias are frequent problems when asking patients to retrospectively recollect events at follow-up time points.

At baseline and 4 weeks, a research team member will also therefore provide each participant with a trial-specific Patient Diary and verbal instructions as to how this could be used. Participants will be advised to use the diary as an aide-memoire to prospectively record adverse events, healthcare resource use (visits to or from healthcare professionals such as GPs, community nurses, hospital admissions etc.) to facilitate completion of questionnaires at the next visit.

9.3.7. End of baseline visit procedures

The research team will ensure the following before the patient leaves the hospital:

- The baseline questionnaires are as complete as possible. If data are missing, any missed questions will be highlighted to the patient.
- The patient has the correct advice leaflet (according to their treatment allocation) and the Patient Diary.
- The patient is aware of when their next appointment is scheduled.

A member of the research team will subsequently ensure that:

- The patient's participation in the trial is appropriately recorded in the hospital records and that hospital notes are labelled / annotated in accordance with local practice.
- The CRF with data collected on delivery of treatment is completed.
- The approved GP letter is sent to the patient's General Practice.

The original completed questionnaires and CRF pages will be sent to PenCTU using FREEPOST envelopes – copies of these should be retained at the local site.

9.4. **4-week follow-up visit (6 weeks post-surgery)**

Participants in both treatment groups will attend a routine six-week post-operative appointment. Participants will have their plaster or support boot removed (unless otherwise indicated), routine clinical assessments and x-rays will be performed to guide the participant's subsequent management. 4-week follow up data will be collected at this visit.

9.4.1. 4-week follow-up questionnaire completion

The participant will be provided with a questionnaire to be completed during the visit. The 4-week questionnaire booklet will comprise:

- EQ-5D-5L (see section 7.2)
- Resource use questionnaire (see section 7.4)

Participants will be encouraged to use their Patient Diary to facilitate answering questions as appropriate.

9.4.2. 4-week follow-up CRF completion

Following removal of the plaster or support boot, the patient will receive routine clinical assessment and a member of the research team will transcribe the following information from the patient's hospital records into the trial case report form (CRF):

- Range of ankle movement (see section 7.2)*
- Weight-bearing status (see section 7.2)
- Circumferential swelling (see section 7.2)*
- Complications and associated antibiotic usage (see section 7.2)
- Time required to remove boot/ or plaster and re-fit if necessary (see section 7.4)
- Mobilisation and adherence to exercise (see section 7.7)

*Range of movement assessments and circumferential swelling measurements must be conducted by a physiotherapist trained in the requirements of the study protocol and documented in the patient's record.

9.4.1. Provision of Patient Diary

Each participant will be provided with a second trial-specific Patient Diary to facilitate completion of questionnaires at the 10-week time point.

9.4.2. End of 4-week follow up visit procedures

A member of the research team will ensure the following before the patient leaves the hospital:

- A copy of the 5-week follow-up questionnaires (and a freepost envelope) will be given to participants. They will be instructed on how to complete the questionnaire using their preferred option (online, phone or post). The importance of completing the questionnaire within 3-10 days will be emphasised. Participants will be encouraged to complete the questionnaire online. If they would prefer not to use the online method, they will be encouraged to complete over the phone. Those participants, who state that they are unable to complete the questionnaire online or by telephone, will use postal completion. Participants who are completing questionnaires online will be emailed to access this approximately 3 days after their 4 week clinic appointment. Participants who have opted for telephone completion will be telephoned approximately 5 days after their 4 week clinic appointment. Participants will be encouraged to have the paper version of the questionnaire by their side during the phone call.
- The patient has their Patient Diary and is aware that they will be receiving questionnaires in approximately 6 weeks' time by post/email and that they may be contacted in the event that the questionnaires are not returned so as to prompt for return or to complete the questionnaire over the telephone.

The research team will also ensure that the patient's continuing participation in the trial is appropriately recorded in the hospital records in accordance with local practice.

Completed questionnaires and CRF pages will be sent to PenCTU using FREEPOST envelopes.

9.5. **5-week follow-up questionnaire completion**

The 5-week follow-up requires participants to complete a questionnaire comprising the following:

- Olerud and Molander (1984) ankle score (see section 7.1)
- EQ-5D-5L (see section 7.2)

The aim is to collect data on primary outcome and EQ-5D-5L at 5 days after the participants 4 week clinic visit. Most participants will have had their plaster / boot removed at the 4 week appointment. It is thought that any benefits resulting from use of the boot would be apparent at this time point. The time window for a valid response will be defined as 3-10 days after the 4 week appointment. The method of data collection has been designed to minimise the risk of missing data. Too much missing data may have a negative impact on the statistical analysis and

interpretation of results (e.g. less precision and possibility of bias). For ease of communication this follow-up will be referred to as the 5 week follow-up.

PenCTU staff will monitor receipt of questionnaires and will issue reminders to patients if the questionnaire has not been returned. If a questionnaire has not been received within 8 days from the week 4 visit, attempts will be made to contact the participant by telephone and the option of completing the questionnaire by telephone will be available.

9.6. **10-week follow-up (12 weeks post-surgery)**

9.6.1. 10-week follow-up questionnaire completion

The 10-week follow-up requires participants to complete a questionnaire comprising the following:

- Olerud and Molander (1984) ankle score (see section 7.1)
- EQ-5D-5L (see section 7.2)
- Resource use questionnaire (see section 7.4)
- Return to activities (see section 7.2)

PenCTU staff will issue questionnaires to participants according to a participant schedule created in the trial database through registration of randomisation and 4-week follow-up dates. The information accompanying the questionnaire will remind participants to make use of their Patient Diaries when completing the questionnaires and request that they are returned within 7 days. The time window for a valid response will be defined as 28 days from the issue of the first week 10 questionnaire. If patients have a preference to receive the questionnaire by post, a self-addressed FREEPOST envelope will be included to facilitate postal return. Participants who have opted to complete questionnaires online will be emailed to access the questionnaire. PenCTU staff will monitor the sending and receipt of questionnaires and will issue another questionnaire with a reminder if the first one has not been returned within 10 days from issue. If a completed questionnaire has not been received by 14 days from issue of the first questionnaire, attempts will be made to contact the participant by telephone. Questionnaires may be completed over the telephone if online/postal questionnaires have not been returned or are lost - if participants feel unable to complete the full questionnaire, participants will have the option of completing a subset of the questionnaire booklet by telephone. Priority will be given to collecting the Olerud & Molander ankle score and EQ-5D-5L.

9.6.2. 10-week follow-up CRF completion

Secondary care healthcare resource use information within the 10 week trial period will be collected and transcribed from the hospital records into the CRF by the local research team. Data extracted will include hospital admissions, outpatient visits, including physiotherapy sessions, day case procedures, visits to Accidents & Emergency departments and diagnostic tests or investigations conducted outside the outpatient visit tariff (See Section 7.4 Resource Use).

A small proportion of patients with complicated recoveries may need further clinical evaluation at 12-weeks post-surgery, as per standard care. The research team will

record the date when the patient was discharged or whether they returned to clinic for further follow up at 10 weeks post baseline (12 weeks-post surgery).

Completed CRF pages will be sent to PenCTU using FREEPOST envelopes.

9.7. **Telephone interviews**

At approximately ten weeks post-baseline, telephone interviews will be conducted by the trial qualitative researcher with up to 20 participants (10 from each treatment group) in order to collect information on patients' experience of their treatment, including psychological and social impact. Telephone interviews will last up to 60 minutes and will be recorded digitally. Further details and description of proposed analysis is given in section 12.3 (Qualitative component).

9.8. **Radiographic Evaluation**

Pre-operative, intra-operative and post-operative X-rays will be taken for each participant as per routine care. In some cases, particularly where recovery is complicated, further X-rays within the 12-week trial period may also be taken. At the end of the study, pre-, intra- and post-operative X-rays, plus any further X-rays taken within the trial period will be reviewed by the CI in a blinded fashion on a participant-by-participant basis. For each participant, the CI will record the following on a bespoke data collection form:

- Fracture classification (Weber A, B or C)
- Fracture pattern (medial malleolar fracture or deltoid ligament injury)
- Integrity of surgical metalwork (displaced or undisplaced)
- Evidence of post-operative fracture healing (yes/no)

The data collection forms will be returned to the CTU for entry into the trial database. Research teams at local sites will liaise with their X-ray departments to arrange anonymisation and transfer of images. Instructions of procedures by which X-rays are collected, labelled, stored and sent are detailed in a separate work instruction.

10. **INTERVENTION DETAILS**

10.1. **Removable support boot**

Patients in the boot group will be fitted with a removable support boot/pneumatic walker brace. To ensure the trial is pragmatic, any model of boot may be used, providing it meets the following specifications:

- Has at least two air cells to provide compression
- Rigid (e.g. plastic) anterior and posterior outer sections. NB: Boots with soft (e.g. foam only) anterior sections are not suitable as they offer reduced support to the ankle
- Suitable for weight-bearing and removable to allow for mobilisation of the ankle

The CI and Lead Site Research Physiotherapist will assess the specifications of support boots prior to their use in the trial to ensure their suitability to deliver the trial intervention.

Patients in the boot group will be given a trial specific advice leaflet advising regular exercise by a physiotherapist trained in the requirements of the protocol e.g. regular removal for exercise during the day/boot off at night as tolerated. The leaflet will provide illustrated instructions for completion of the following exercises; Straight leg raise, Ankle dorsiflexion/plantarflexion, Ankle inversion/eversion, Calf stretch, and Resisted plantarflexion. Patients will be encouraged to mobilise their ankle as often in a day as pain allows (recommended at least 3 times a day.)
Participants will be advised on gait re-education with crutches and will progress to weight-bearing as able.

10.2. **Plaster Cast**

The plaster cast used will be a standard below knee rigid plaster cast shell with soft lining to provide support in a fixed position to the ankle. The plaster cast is rigid enough to support weight-bearing and is custom built for the patient.

The plaster group will also receive a trial specific advice leaflet on plaster care/mobilisation of free joints. The leaflet will provide illustrated instructions of the following exercises: Toe flexion/extension, Static quads and Straight leg raises. Patients will be encouraged to mobilise their ankle as often in a day as pain allows (recommended at least 3 times a day.)
Participants will be advised on gait re-education with crutches and will progress to weight-bearing as able.

10.3. **Associated Risks**

The risks associated with participating in the ART study are no different to the risks of receiving standard treatment outside the study.
However, known complications include: blisters, pressure sores, failure of fixation, operation/revision surgery, wound infections, compartment syndrome, deep vein thrombosis (DVT), nerve injury, wound breakdown, and pulmonary embolism.

Participants randomised to plaster may experience more pressure sores, stiffness, difficulty accessing and monitoring wounds and similarly, participants in a support boot may experience problematic wounds.

11. **ASSESSMENT OF SAFETY**

11.1. **Standard definitions**

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment.

Adverse reactions (AR) are defined as an event that is considered to have a suspected causal relationship to the trial intervention (plaster or support boot.)

Serious adverse events (SAE) are defined as any untoward and unexpected medical occurrence that:

- Results in death
- Is life-threatening[1]
- Requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

11.2. Reportable events

In the ART trial, all SAEs (as defined above) will be reported to PenCTU regardless of causality. Events which are not serious will not be collected or reported as adverse events but complications listed in section 10.3 will be reported as outcome measures.

11.3. Procedures for Serious Adverse Event reporting

Procedures for collecting and reporting SAEs will be described in a separate trial-specific Work Instruction and will be discussed during investigator site initiation meetings.

SAEs may be identified via patient report at clinic visits or from receipt of resource use questionnaires which indicate a hospital admission. All SAEs will be reported to CTU using a bespoke Serious Adverse Event reporting form (SAE form). PIs or delegated staff must fax/email the completed SAE form to CTU within 24 hours of becoming aware of the event. The SAE report form will include a description of the event and an assessment of severity and causality as described below. PenCTU will maintain a register of all reported SAEs.

11.3.1. Assessment of severity and causality

All SAEs must be assessed for severity by the PI(s) or by those members of the research team specifically authorised by the Principal Investigator(s) to assess SAEs, as documented in the site delegation log. Assessments of severity will be made according to the following conventions:

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with every day activities

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

Severe: An event that prevents normal everyday activities

The term ‘severe’, used to describe the intensity of an event or reaction, should not be confused with the term ‘serious’ which is a regulatory definition. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

[1] Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.[20]

An assessment of the causal relationship between an SAE and trial participation will be made according to the standardised guidance given in Table 2 below:

Table 2: Definitions of Causality

Relationship	***Description***
Unrelated	*There is no evidence of any causal relationship*
Unlikely	*There is little evidence to suggest there is a causal relationship (e.g. The event did not occur within a reasonable time after administration of the trial treatment/procedure). There is another reasonable explanation for the event (e.g. The participant's clinical condition, other concomitant treatment).*
Possible	*There is some evidence to suggest a causal relationship (e.g. Because the event occurs within a reasonable time after administration of the trial treatment/procedure). However, the influence of other factors may have contributed to the event (e.g. The participant's clinical condition, other concomitant treatments).*
Probable	*There is evidence to suggest a causal relationship and the influence of other factors is unlikely.*
Definitely	*There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.*

11.3.2. Assessment of expectedness

SAEs deemed to be possibly, probably or definitely related to trial participation will be classified as SARs. In such cases, the PI or authorised delegate will make a judgement on whether the event is expected or unexpected. The assessment of expectedness will be made with reference to the known risks listed in section 10.3. An event will be classed as unexpected if it is not listed in protocol section 10.3.

11.4. **Processing Serious Adverse Event report forms**

On receipt of a completed SAE form, PenCTU will assign a unique SAE number and confirm receipt of the event to the reporting site and to the study Sponsor. Staff from the reporting site will file the receipt confirmation and the original SAE report form in the relevant participants CRF. Any further correspondence relating to the same event (e.g. data query forms) must also be filed with the original form.

If incomplete information is available at the time of reporting, all appropriate information relating to the SAE will be forwarded to PenCTU as soon as possible. All serious adverse events will be followed up until resolution.

11.4.1. Onward reporting

SAEs will be reported on a periodic basis to the Sponsor, CI and Trial Steering Committee in order to maintain sufficient oversight of trial safety.

SAEs deemed related to the trial procedures and which are unexpected are subject to expedited reporting; they will be notified to the Research Ethics Committee (REC) within 15 days for a non-life threatening event and within 7 days for a life-threatening event. Such events will be reported to the Trial Steering Committee on an ongoing basis.

12. STATISTICS AND DATA ANALYSIS

12.1. Sample Size Calculation

The study is powered to detect a 10-point difference in ankle score since patient and public involvement indicated that walking without aids/getting back to work were the most important issues. A change from support with a stick/crutch to no support and a change to getting back to normal work/activities of daily life from simpler or part-time work are both associated with a 10-point change on the Olerud and Molander[14] subjective scale (primary outcome).

An estimate of standard deviation of the ankle score six weeks post-surgery was derived from an audit of 18 patients having plaster casts at Poole Hospital. This figure of 21.9 is very similar in magnitude to those reported in the Cochrane review[13]. Based on an unpaired t-test with two groups of equal size, assuming 90% power, a two-sided 0.05 significance level, a standard deviation of 21.9 and a mean difference of 10 points between the plaster and boot groups, a total sample size of 204 (102 in each group) is required[21]. The study will over-recruit by 20%[22] to allow for non-responders, or missing data, not to contribute data to the main analysis. However it is anticipated that the true percentage will be reduced by offering flexible methods of completion; either online, post or by phone. As the study progresses, the percentage with missing primary outcome data will be monitored and discussed at regular trial management group meetings and reductions/ increases in over-recruitment will be made accordingly so that the target of 204 with completed data is met.

The study will aim to recruit 246 patients in total (123 in each group) over a 2 year recruitment period.

12.2. Description of statistical methods

A detailed Statistical Analysis Plan will be developed and signed off by the Trial Steering Committee before any analyses commence. The anonymised data will be analysed by 'intention to treat' (i.e. patients will be analysed in the treatment arm they were randomised to, even if they received something else, or swapped treatments). The analysis and initial write-up will be blinded to the treatment groups and will report according to the Consolidated Standards of Reporting Trials[23-24], including a participant flow chart. No imputation methods for missing data will be used for the main effectiveness analyses.

12.2.1. Baseline descriptives:

Baseline descriptive data on demographics (gender, age, marital status, whether living alone, highest educational level, employment status, driving status), fracture characteristics (fracture classification, pattern, complexity), BMI, Olerud and Molander ankle score pre-injury, and EQ-5D will be presented overall and for both groups separately. This will help with (a) assessment of external validity of the trial, and (b) to see whether the 2 groups were comparable at baseline (no significance tests will be conducted). The Olerud and Molander scale includes a question on activity compared to before injury. This would make this question confusing to complete at baseline, and so for baseline only this question has been dropped and

all participants will be given the maximum score of 20 for this question (i.e. the score for work and activities same as before injury).

12.2.2. Primary outcome:

The primary outcome is the Olerud and Molander[14] ankle score (measured out of 100) five weeks post-baseline. Questionnaires that were not completed in the 3-10 day time window will be treated as missing data.

Multiple regression including study site, age and fracture complexity as a factor will be used to compare mean ankle score at five weeks post-baseline between the plaster and boot groups.
Instead of implementing stratification of age and fracture complexity at randomisation (which in any case could be problematic if there is a large number of strata with a relatively small sample size), the potential issue of imbalance in age and fracture complexity between the two arms of the trial will be addressed by adjusting (stratifying) for the covariates of age (as a continuous variable) and fracture complexity in the analysis. Thus the proposed analysis of the primary outcome, for example, will use multiple regression and, in addition to treatment arm, include the pre-specified variables of study site, age and fracture complexity.

Two groups are proposed regarding fracture complexity: Simple fibular fracture and comminuted fracture. If the fibular fracture has a single fracture line with two discrete fragments only, it comprises a 'simple' fracture. If the fibula has more than one fracture line and therefore more than two discrete fragments that require accurate reduction to achieve stability, it comprises a comminuted fracture. The pattern and complexity of the fracture can influence the choice of hardware used by the surgeon to achieve stability. Simple fractures are fixed with unlocked plates whereas complex fractures can require more sophisticated and expensive locked plates.

The pre-baseline measure is collected retrospectively and so has not been included in the primary analysis. By ten weeks post-baseline, it is anticipated that both groups will be similar on the primary outcome, and so this has not been included in an overall repeated measures type analysis. The five week post-baseline data collection period is the critical period, as this is when it is anticipated that the group who had boots will have a greater level of function[3,6].

Some additional analyses (including sensitivity analyses) on primary outcome will also be conducted:
(a) It is acknowledged that some participants (in either group) will leave the 4 week appointment with a plaster cast or boot, and so will complete the scale whilst still wearing the plaster/ boot. In a supplementary sensitivity analysis these participants will be excluded from the analysis to see if the results change.
(b) Pre-injury Olerud and Molander scale will be included as a covariate.
(c) Whether or not the patient had a medial malleolar fracture will be included as a covariate
(d) Any baseline variables that appear, by chance, to differ between the groups will be added in as covariates.
(e) The effectiveness of the intervention may vary across different subgroups (strata) of patients (e.g. age and fracture complexity). Therefore for each outcome

supplementary statistical analyses are proposed in which it is tested whether there is a statistical interaction between age and treatment arm and between fracture complexity and treatment arm. It is however acknowledged that statistical power will be reduced for these significance tests and they will be considered to be exploratory. Age will be grouped as: under 65 years of age at the time of fracture and 65 + years.
(f) The main analysis will use an "intention to treat" approach. As a supplementary analysis two sets of "per protocol" analyses will also be conducted. In the first of these, patients will be analysed according to the method (boot or plaster) that they actually wore. If patients crossed over from one to the other during the 4 week period they will be excluded from the per protocol analysis. If patients didn't wear the boot/ plaster for the full 4 weeks they will be excluded. In the second analysis participants will additionally be excluded if they didn't perform the exercises recommended. Thus if they performed the exercises less than once per day they will be excluded
(g) Data on primary outcome completed outside of the 3-10 day window will be included in the analysis
(h) The robustness of the results to missing data will be assessed by repeating the analysis incorporating the imputed values that will be derived as part of the economic analysis (see section 12.4)

The study will also compare the ten week Olerud and Molander Ankle score between groups to check whether any differences still remain at 10 weeks.
To see whether patients in both groups have returned to pre-injury levels of function we will calculate the mean difference (95% CI) between pre-injury and 10 week values for each group, and the proportion of patients whose score is worse by 10 points or more. These statistics will also be compared between groups.

12.2.3. Secondary outcomes:

The profiles from the patients' answers to the EQ-5D-5L will be weighted using the EuroQol's published United Kingdom societal utility tariffs to produce a composite, utility based quality of life score and EuroQol has piloted the 5L valuation scores[25]. If final scores are not available by the end of the trial, the crosswalk developed by EuroQol from the three level scores will be used. Quality Adjusted Life Years will then be created from the four time point utility scores assuming a linear change between the time points and using the area under the curve approach. Incremental QALY gains between arms will then be estimated using regression analysis adjusted for baseline utility and site, age and fracture complexity variables.

Multiple regression will be used to investigate differences between the two groups in the other continuous outcomes measured at four weeks post-baseline (e.g. degrees of range of movement (dorsiflexion, plantarflexion, inversion, eversion), circumferential swelling and 10 weeks (e.g. return to daily activities on 0-10 scale). Complications in the two groups (presence and severity), healing status (displaced / undisplaced and evidence of post-operative fracture healing (yes/no)), employment status at 10 weeks, driving status and weight bearing status will be investigated using logistic regression (binomial or multinomial depending on the number of categories), again taking study site, age and fracture complexity into account. Survival analysis will be used to investigate the time from randomisation to starting to drive again. Supplementary analysis (b) to (e) as described for the primary outcome will also be conducted for secondary outcomes.)

12.3. Qualitative Component

At approximately ten weeks post-baseline, telephone interviews will be carried out with up to 20 participants or until data saturation. A maximum variation strategy will be used to capture a range of experiences of participants receiving each treatment. Telephone interviews will last up to 60 minutes, will be recorded digitally, and were chosen to reduce costs and for convenience to the patients. The topic guide has been developed through collaboration with service users, and addresses:

- Experiences of each type of treatment (plaster/boot).
- Lifestyle implications – individual (e.g. washing), family (including caregivers, as requested by feedback from patient and public involvement), social, psychological, work, financial, residential, transport (e.g. driving), diet, leisure activities, and independence.
- Expectations, mind-set, confidence, including the perceived views of their carers as suggested by the patient and public involvement.

The telephone interviews will be transcribed verbatim, anonymised, and coded using Thematic Analysis[26]. A second researcher will analyse a selection of transcripts to validate the codebook/coding. It is anticipated that the findings from this qualitative study will enhance the results by explaining the psychological and social impact of each treatment.

12.4. Economic Evaluation

The primary economic evaluation will compare the costs and health benefits of the support boot compared to plaster in short-term ankle fracture management from an NHS and Personal Social Services perspective. In sensitivity analysis, an economic evaluation from a societal perspective on costs will be performed.

The evaluation will be:

1. A cost-utility analysis at ten weeks post-randomisation; Quality Adjusted Life Years (QALYs) between arms will be compared to identify whether any treatment arm is dominant (i.e. less costly and more effective). If no arm is dominant, results will be presented as a bootstrapped incremental cost-effectiveness ratio (ICERs) with respect to QALYs gained. Bootstrapped estimates of costs and effects will be plotted in the cost-effectiveness plane. Incremental net monetary benefit statistics (INMB) will be derived using the £20,000 and £30,000 societal willingness to pay thresholds for a QALY. Cost-Effectiveness Acceptability Curves (CEACs) will be plotted to show the probability of the intervention being cost-effective at a range of societal willingness to pay thresholds, thus addressing uncertainty around the adoption decision. If one arm is dominant, ICERs are not meaningful and we will only report INMB statistics and plot the cost-effectiveness planes and CEAC.

2. A cost-effectiveness analysis at approximately 5 weeks post-baseline, coinciding with the collection of primary clinical outcome; Costs and Olerud and Molander scores between arms will be compared to identify whether any treatment arm is dominant. If no arm is dominant, results will be presented as a bootstrapped incremental cost-effectiveness ratio with respect to the Olerud and Molander[14] scale. If the treatment arm is a dominant or dominated strategy, ICERs will be

negative and not meaningful. In that case, we will only report INMB statistics in relation to QALYs and will not proceed any further with the cost-effectiveness analysis with respect to the Olerud and Molander scale.

Collecting 5 week and 10 week resource use:

Resource use collection will take place as defined in above section “7.4 Resource Use” in this protocol.

At 10 weeks, resource use for the primary economic result will result from adding secondary care resource use collected from the review of 10 weeks of medical notes and the two resource use questionnaires at 4 weeks and 10 weeks.

For the second economic result, the primary clinical outcome collected at approximately 5 weeks (4 weeks + 3-10 days) after randomisation will be compared with costs for the same period. We will identify the proportion of secondary care cost, collected from medical notes, taking place in the additional days post the 4 week clinic visit for the patient, and assume the patient would have an equal proportion of cost for the other cost categories, collected by questionnaire. This assumed incremental patient reported cost, will be added to the 4 week cost data collected from questionnaires and the corresponding period cost from medical notes, to compose a total patient cost from baseline to collection of primary clinical outcome data.

Valuing resources:

Resource use will be valued using unit costs for health and social care, department of health reference costs or other national routine sources[27-30]whenever available. Trust finance departments will be contacted for procurement costs on the boot and plaster materials. Productivity losses will measure absenteeism and presenteeism and be valued using the human capital approach[31-32] in the main analysis, and the friction costs approach in sensitivity analysis. Estimations will be adjusted for pre-randomisation work status and return to work.

Analysis of costs and outcomes:

Costs and QALYs (mean and confidence intervals) will be estimated using regression analysis, adjusting for site, age, and fracture complexity in addition to baseline utility for QALYs). We will ascertain whether the treatment arm would be dominant, i.e. less costly and more effective, or dominated, i.e. more costly and less effective, with respect to QALYs and the Olerud and Molander scale.

Missing data in the economic result:

Cost is cumulative and additive: missing data in one cost component at one follow-up time point means that the full cost per patient cannot be computed. A specific missing data strategy has been developed for the economic evaluation, in case of poor patient-completion of resource use questions.

Missing data will be imputed using multiple imputation methods, in a two-stage ordinary least squares model, adjusting for socio-demographic characteristics

collected at baseline. As the primary economic result are parameters (ICERs / NMB) relating Costs and QALYs, the imputation models will simultaneous include disaggregated cost categories and utilities.

If less than 30% of the cost and QALY data is missing, the main economic analyses will report the complete case scenario. If more than 30% of data is missing, the main economic analysis will report the primary economic result using the completed imputed dataset, with the complete case scenario as the secondary analysis. Should the secondary analysis using the primary clinical outcome require imputation, imputed value sets from the statistical analysis will be used to estimate the economic result parameters.

Sensitivity analysis:

One way and scenario sensitivity analysis will be used to address uncertainty of costing and methodological assumptions. These may include, for example, adding a societal perspective to the primary NHS+PSS (prescribed specialised services) result, valuing productivity losses using a different approach (i.e. friction cost), and costing assumptions for the 3 to 10 days incremental cost period not directly captured in questionnaires. Results will be presented disaggregated by perspective (i.e. National Health Service/patients/societal) for clear decision-making information.

13. ETHICAL, REGULATORY, ADMINISTRATIVE AND QUALITY ASSURANCE

13.1. Ethical considerations

This trial was designed around the patient pathway and the usual management of ankle fractures within National Health Service Trusts, and therefore raises no special ethical issues. Staff will be trained in Good Clinical Practice which will be followed at all times.

An application for ethics approval will be made to a National Research Ethics Service Committee (REC). The trial will not proceed until Ethics approval and Trust approval from each participating site is obtained. Any amendments to the protocol will be submitted for REC approval and local NHS approval as appropriate.

Annual progress reports will be submitted to the REC using the recognised National Research Ethics Service (NRES) template. An end-of-trial declaration will be provided to the REC within 90 days of trial conclusion or within 15 days of trial termination in the event the trial is prematurely terminated.

Since the trial involves no Investigational Medicinal Product or non-CE marked medical devices, authorisation from the Medicines and Healthcare products Regulatory Agency will not be sought.

13.2. Declaration of Helsinki

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP.

13.3. Research Governance

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, NHS Research Governance Framework for Health and Social Care (2005 2nd edition) and other regulatory requirements as appropriate.

13.4. Study Management

The Trial Manager will co-ordinate the study (overseen by the Chief Investigator, supported by the Bournemouth University Clinical Research Unit and Peninsula Clinical Trials Unit). The Peninsula Clinical Trials Unit is a United Kingdom Clinical Research Collaboration registered Clinical Trials Unit and will conduct randomisation and manage the data following their Standard Operating Procedures.

Bournemouth University will support both the quantitative and qualitative analysis, the University of Bristol will support economic analysis, and Peninsula Clinical Trials Unit will provide randomisation, data management services and senior trial management support. The CI will be responsible for the overall running of the trial and will be in regular contact with PIs at the other participating sites.

The Trial Management Group (TMG) chaired by the Chief Investigator, will include all co-applicants, Trial Manager and service user representatives. The TMG will take responsibility for monitoring progress, ensuring development of documentation and forms, monitoring participant recruitment, follow-up and budget, discussing analysis, results, draft reports and dissemination. The TMG will meet regularly prior to the start of the study, and then in person every six months and remotely in between. There will be no Data Monitoring Committee (DMC) since both treatments are used in clinical practice.

13.5. Trial Steering Committee

The Trial Steering Committee (TSC) is responsible for the overall supervision of the trial, including overseeing recruitment, ensuring milestones are achieved and general scientific probity is maintained. In the absence of the DMC, the TSC will take on the role of reviewing adverse events, maintaining safety and will make recommendations for the premature discontinuation of the study where necessary.

The TSC will be chaired independently and will comprise of 6 full members; 3 independent experts (clinician(s)/statistician(s)), the Chief Investigator, and a service user representative. The Trial managers, data manager, sponsor and a funder representative will be invited to TSC meetings as observers. Members will meet at least annually as part of the Trial Steering Committee and will follow functions according to the Medical Research Council Good Clinical Practice guidelines[33]. The composition and function will be described in a TSC charter prepared prior to study commencement.

13.6. Monitoring

Continuous data monitoring will be undertaken by the study team. Monitoring visits to all sites will also be conducted to check protocol compliance during the study, and as required where problems/potential problems are identified. The frequency and extent of monitoring visits will be described in a monitoring plan, the first version of which will be finalised prior to participant recruitment. Visits will be carried out by the Trial Manager and/or the Sponsor's quality assurance staff. Relevant trial-related documents will be made available by the PIs and research team for monitoring.

13.7. Audit and Inspection

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data and essential documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.
In the event of the site being notified directly of a regulatory inspection, the sponsor requests the investigator to notify the sponsor.

14. DATA HANDLING AND RECORD KEEPING

14.1. Participant Numbering

Upon randomisation, each participant will be allocated a unique trial number and will be identified in study documentation by his/her trial number and initials.

14.2. Source data

The first record of any study related visit or assessment should be recorded in the patient's medical record or patient questionnaire, which becomes the source data. Data from source documents will be transcribed into study specific CRFs by authorised personnel on the delegation log. All X-ray images will be anonymised and transferred securely via The Image Exchange Portal (IEP) or by anonymised CD.

14.3. Data Entry

Data will be recorded on study-specific case report forms (CRFs). Completed CRFs will be sent to the PenCTU for double-data entry on to a password-protected database accessed via the Internet. Forms will be tracked using a web-based trial management system. Double-entered data will be compared for discrepancies using a stored procedure. Discrepant data will be verified using the original paper data sheets. The data manager will also coordinate the sending, tracking, receipt and entry of patient questionnaires.

Anonymised socio-demographic, outcome and resource use data will be shared with Bournemouth University and the University of Bristol for analysis to be performed.

14.4. Data confidentiality and security

Investigators will ensure that the patients' anonymity is maintained on all documents. Data will be collected and stored in accordance with the Data Protection Act 1998.

PenCTU will store anonymised study data in locked filing cabinets within a locked office. Electronic records will be stored in a SQL server database, stored on a restricted access, secure server maintained by the University of Plymouth. The website will be encrypted using SSL. Direct access to the trial data will be restricted to members of the research team and the CTU, with access granted to the Sponsor on request. Copies of original study data retained at study sites will be securely stored for the duration of the study prior to archiving.

14.5. Archiving

Following completion of trial data analysis, data and essential documentation will be archived in a secure location for at least five years after the end of the trial, in accordance with the Sponsor's standard operating procedure. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so.

15. FINANCE, INDEMNITY AND INSURANCE

15.1. Funding

The study will be funded by the NIHR Research for Patient Benefit (RfPB) Grant, reference number; PB-PG-0213-30021. Poole Hospital will centrally manage the financial arrangements in accordance with National Institute for Health Research, Research for Patient Benefit and Trust requirements.

15.2. Sponsor

The study is sponsored and coordinated by Poole Hospital NHS Foundation Trust.

15.3. Indemnity

Poole Hospital NHS Foundation Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England. Standard NHS cover for negligent harm is in place. There are no specific arrangements to cover for non-negligent harm.

16. PUBLICATION POLICY AND INTELLECTUAL PROPERTY

16.1. Publication Policy

The results of the study will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals. The Trial Management Group will produce a publication policy which will outline the intended outputs, authorship and contribution, target outlets.

If the participants would like to be informed of the results of the study, they can be sent a plain English summary of the study results after the end of the study.

16.2. Intellectual Property

Arrangements with collaborating sites will be in accordance with the relevant clauses from the NIHR standard template for non-commercial studies. Intellectual Property rights will be described in agreements between the sponsor and collaborating institutions.

17. REFERENCES

1. Donaldson LJ, Reckless IP, Scholes S, Mindell JS, Shelton NJ. The epidemiology of fractures in England. *Journal of Epidemiology and Community Health* 2008;62(2): 174-180.

2. Lloyd J, Lockhart J, Sisak K, Middleton R. How to cut overnight stays and improve trauma pathways. *Health Service Journal* 2012. http://m.hsj.co.uk/5041062.article (accessed 11 January 2013).

3. Thomas G, Whalley H, Modi C. Early mobilization of operatively fixed ankle fractures: a systematic review. *Foot and Ankle International* 2009;30(7): 666-674.

4. Shaffer MA, Okereke E, Esterhai JL Jr, Elliott MA, Walker GA, Yim SH, Vandenborne K. Effects of immobilization on plantar-flexion torque, fatigue resistance, and functional ability following an ankle fracture. *Physical Therapy* 2000;80(8): 769–780.

5. Stevens JE, Walter GA, Okereke E, Scarborough MT, Esterhai JL, George SZ, Kelley MJ, Tillman SM, Gibbs JD, Eilliot MA, Frimel TN, Gibbs CP, Vandenborne K. Muscle adaptations with immobilization and rehabilitation after ankle fracture. *Medicine and Science in Sports and Exercise* 2004;30(10): 1695–1701.

6. Vioreanu M, Dudeney S, Hurson B, Kelly E, O'Rourke K, Quinlan W. Early mobilisation in removable cast compared with immobilisation in a cast after operative treatment of ankle fractures: a prospective randomised study. *Foot and Ankle International* 2007;28(1): 13-18.

7. Simanski C, Maegele M, Lefering R, Lehnen D, Kawel N, Riess P, Yücel N, Tiling T, Bouillion B. Functional treatment and early weight-bearing after an ankle fracture; a prospective study. *Journal of Orthopaedic Trauma* 2006;20(2): 108-114.

8. Dogra AS, Rangan A. Early mobilisation versus immobilisation of surgically treated ankle fractures. Prospective randomised control trial. *Injury* 1999;30(6): 417-419.

9. Lehtonen H, Jarvinen T, Honkonen S, Nyman M, Vihtonen K, Jarvinen M. Use of a cast compared with a functional ankle brace after operative treatment of an ankle fracture. A prospective, randomized study. *Journal of Bone and Joint Surgery* 2003;85(2): 205-211.

10. Farsetti P, Caterini R, Potenza V, De Luna V, De Maio F, Ippolito E. Immediate continuous passive motion after internal fixation of an ankle fracture. *Journal of Orthopaedics and Traumatology* 2009;10(2): 63-69.

11. ISRCTN Register. *A trial comparing weight-bearing to non-weight-bearing following ankle fracture fixation.*

http://www.controlledtrials.com/mrct/trial/printfriendly/2293127 (accessed 11 January 2013).

12. US National Institutes of Health. *Early Weight-bearing and Mobilization versus Non-Weight-bearing and Mobilization in Unstable Ankle Fractures.* http://clinicaltrials.gov/ct2/show/nct01196338 (accessed 11 January 2013).

13. Lin CW, Moseley AM, Refshauge KM. Effects of rehabilitation after ankle fracture: a Cochrane systematic review. *European Journal of Physical and Rehabilitation Medicine* 2009;45(3): 431-441.

14. Olerud C, Molander H. A scoring scale for symptom evaluation after ankle fracture. *Archives of Orthopaedic and Traumatic Surgery* 1984;103(3): 190-194.

15. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M *EQ-5D-5L User Guide. Basic Information on How to Use the EQ-5D-5L Instrument.* Version 1.0. EuroQol Group Executive Office on behalf of the EuroQol Group. Rotterdam: EuroQol Group; 2011. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/ UserGuide_EQ-5D-5L.pdf (accessed 31 October 2011).

16. Reilly Associates. *WPAI: GH V2.0.* http://www.reillyassociates.net/WPAI_GH.html (accessed 04 December 2012).

17. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire – general health version in patients with rheumatoid arthritis. *Arthritis Research and Therapy* 2010;12(5): R177.

18. Braakman-Jansen LMA, Taal E, Kuper IH, van de Laar MAFJ. Productivity loss due to absenteeism and presenteeism by different instruments in patients with RA and subjects without RA. *Rheumatology* 2012;51(2): 354-361.

19. Weber BG. *Die Verletzungen Des Oberen Sprunggelenkes.* Second edition. Berne: Verlag Hans Huber; 1972.

20. European Commission, Detailed guidance on the collection, verification and presentation on adverse reaction reports arising from clinical trials of medicinal products for human use, ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL, May 2006, http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf (accessed 10 June 2014.)

21. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods* 2007;39(2): 175-191.

22. Sackett DL, Straus SE, Scott Richardson W, Rosenberg W, Haynes RB. *Evidence-Based Medicine. How to Practice and Teach EBM.* Second Edition. Edinburgh: Churchill Livingstone, Harcourt Publishers Limited; 2000.

23. Moher D, Hopewell S, Schultz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger, M, Altman DG. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal* 2010;340: e1-28.

24. Schulz KF, Altman DG, Moher D for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *British Medical Journal* 2010;340: 698-702.

25. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ- 5D-5L). *Quality of Life Research* 2011;20(10): 1727-1736.

26. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3(2): 77-101.

27. Curtis L. *Unit Costs of Health & Social Care 2011*. Canterbury: Personal Social Services Research Unit; 2011. http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf (accessed 16 January 2013).

28. Department of Health. *NHS 2010-11 Reference Costs Publication;* 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131160.pdf (accessed 11 January 2013).

29. British Medical Association, Royal Pharmaceutical Society of Great Britain, Joint Formulary Committee. *British National Formulary*. 62nd Edition. London: Pharmaceutical Press; 2011.

30. Office for National Statistics. *Average Weekly Earnings Dataset* 2011. http://www.ons.gov.uk/ons/rel/lms/labour-market-statistics/october-2011/earnings-tsd-dataset.html (accessed 11 January 2013).

31. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *Journal of Health Economics* 1995;14(2): 171-189.

32. van den Hout WB. The value of productivity: human-capital versus friction-cost method. *Annals of the Rheumatic Diseases* 2010;69(Supplement I): i89-i91.

33. Medical Research Council. *MRC guidelines for good clinical practice in clinical trials.* MRC Clinical Trials Series 2010. http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416 (accessed 11 January 2013).