EXACT: EXercise or Advice after ankle fraCTure

Ankle fracture is one of the most common injuries of the lower limb. Initial management consists of surgical or conservative orthopaedic treatment and a period of immobilisation in a cast or brace. Subsequently, the presence of pain, stiffness, weakness and swelling impairs the performance of everyday activities and results in significant activity limitation and participation restriction. Rehabilitation programs are often provided to address the health consequences of the fracture and the subsequent immobilisation. Provision of these rehabilitation services involves an enormous investment of health resources. There have, however, been no randomised trials of the effectiveness of a comprehensive rehabilitation program after removal of immobilisation for ankle fracture, so the effectiveness of rehabilitation after ankle fracture is not known.

We will conduct a definitive randomised controlled trial to determine the effects of a rehabilitation program on activity limitation and quality of life. The intervention will be applied to people with ankle fracture initially treated with a period of immobilisation. The findings of the trial will provide fundamental information to support evidence-based decisions about the treatment of ankle fracture.

Aims

The aim of the trial is to determine whether a rehabilitation program (involving supervised exercise, gait training, and advice) is more effective and cost-effective than the provision of general advice about exercise after immobilisation for ankle fracture. The hypothesis is that rehabilitation will reduce activity limitation and improve quality of life, on average, compared to advice. We will also determine if treatment effects are influenced by fracture severity and by the age and gender of participants.

Background

Ankle fracture (fracture of the distal tibia and/or fibula) is the second most common ankle injury after ankle sprain [1]. Those at highest risk of ankle fracture are young men and, to a lesser extent, older women [2]. The incidence of ankle fracture per 10,000 population per annum is 13 to 28 for young men and 16 to 20 for older women, with a rate of at least 5 per 10,000 per annum across all ages [2,3]. If these stratum-specific rates are applied to the Australian population [4] there would be over 20,500 ankle fractures in Australian adults each year, which is similar to the number of hip fractures each year [5].

Orthopaedic management is dependent on the severity of the fracture, but generally involves immobilisation of the ankle in a cast or a brace for about 6 weeks [6]. Surgical fixation is required in about 50% of cases [7,8].

The disabling sequelae of ankle fracture and the subsequent immobilisation frequently prevent return to work and sport. In our recent trial of management of ankle fractures [7] participants had significant activity limitation when their immobilisation was ceased (mean Lower Extremity Function Scale score = 33.6, where no activity limitation receives a score of 80) [9]. One-third of participants were unable to walk without an aid because of pain and stiffness. Participants reported that they had returned to 41% of their usual work activities and only 13% of their usual recreation activities, on average.

Rehabilitation programs are often provided to address the sequelae of the ankle fracture and immobilisation, including pain [7,8], stiffness [10,11], weakness [12-14], and swelling [15,16]. Rehabilitation can commence as soon as the fracture has been stabilised, so it may be provided during the period of immobilisation. (This may be achieved by wearing a brace to immobilise the ankle. The brace can be removed to allow gentle ankle exercise.) More often rehabilitation programs are provided after the period of immobilisation. Typically such programs consist of stretch, manual therapy, exercise, gait training and advice [7,8].

There is limited evidence on the effects of rehabilitation interventions. We recently completed a Cochrane systematic review to evaluate conservative interventions after ankle fracture [17]. The
review found some evidence that commencing weight bearing and the use of a type of immobilisation that can be removed (e.g. a brace) to allow exercise during the immobilisation period may improve outcome after ankle fracture. Of 31 randomised trials identified, only two trials [8,18] investigated interventions provided after ceasing immobilisation, a critical time for rehabilitation. One trial was conducted by our research team [7,8]. We have just completed another trial [7] and a trial evaluating rehabilitation after immobilisation for surgically treated ankle fracture has recently been published [19], neither of these trials were included in our Cochrane review.

In the first of our two trials we showed that adding passive stretch (either 6 minutes/day or 30 minutes/day) to an exercise program did not reduce activity limitation or increase ankle range of motion compared to exercise alone [8]. In the second trial we confirmed the findings of an earlier, small trial [18] which showed adding manual therapy (large amplitude [grade III] anterior-posterior glide of the talus) to an exercise program did not improve activity limitation or quality of life, or yield economic benefits, compared to exercise alone [7]. Both of our trials were adequately powered, so we were able to rule out clinically worthwhile effects of both interventions. These trials provide strong evidence of a lack of effect of two major components of rehabilitation programs after ankle fracture.

The obvious question that arises from these trials is whether the remaining components of the rehabilitation program – supervised exercise, gait training and advice – produce clinically important effects. More generally, these trials raise the question of whether rehabilitation improves outcomes after ankle fracture. Even though rehabilitation programs are provided to about 70% of patients after the cessation of immobilisation [7,8], there has been only one randomised trial comparing rehabilitation programs with the alternative of providing advice and simple exercise at the point of cessation of immobilisation [19]. A non-randomised comparison suggests that participation in a rehabilitation program after immobilisation for ankle fracture produces slightly better outcomes (mean of 6.2 points more activity on a 80-point scale, 95%CI 2.5 to 9.9) compared to no formal rehabilitation [20]. One randomised trial comparing exercise rehabilitation to usual care after cast immobilisation for surgically treated ankle fractures concluded that exercise rehabilitation and usual care produced similar outcomes at 6 months (mean between-group difference of -1.1 points on a 100-point scale, 95%CI -10.0 to 7.8) [19]. Furthermore, a small (N=56) clinical trial that recently compared a rehabilitation program to brief advice after immobilisation for wrist fracture [21] found rehabilitation produced slightly better outcomes (mean difference in activity of 13 points on a 100-point scale, 95%CI 2-24) compared to advice alone. Thus the limited available data provide grounds both for optimism and pessimism about the effects of rehabilitation after ankle fracture. We need clarification of the effects and costs of rehabilitation after ankle fracture if we are to provide evidence-based treatment for this problem.

A definitive randomised controlled trial is required to determine whether rehabilitation (supervised exercise, gait training and advice) provided in the period soon after immobilisation improves outcomes. Such a trial is the logical culmination to the series of trials we have conducted. The trial will determine whether rehabilitation services should be provided after ankle fracture.

There may be sub-groups of people with ankle fracture who may benefit more from rehabilitation. As indicated above, the incidence of ankle fracture is high among older women [2,3]. It is widely known that osteoporosis increases the risk of fractures of the spine, hip and wrist, but it is less widely appreciated that osteoporosis also increases the risk of ankle fracture [22]. Older (postmenopausal) women are more likely to have osteoporosis [23]. Physical performance [24] and physical activity [25] also decline in age. Participation in a rehabilitation program may, therefore, particularly benefit this sub-group of older women (aged over 50 years). Furthermore, the severity of fracture has been found to influence outcome in ankle fracture [20]. It is unclear whether rehabilitation should be provided to all people after ankle fracture, or if it should be selectively administered to those with more severe fractures. In our trial we will determine if treatment effects are influenced by fracture severity and by the age and gender of participants.
It is important to understand the costs as well as the consequences of rehabilitation after ankle fracture. To date only one trial has included an economic evaluation of conservative interventions provided after immobilisation for ankle fracture [7]. The average cost of outpatient treatment after immobilisation was AUD 735 (SD 876) per person over 24 weeks. Outpatient physiotherapy accounted for the highest costs in both direct healthcare (38.6%) and out-of-pocket costs (41.7%) for these patients. In this study we plan to undertake both cost-effectiveness and cost-utility analyses. In a cost-effectiveness analysis, consequences are measured in natural units, whereas in a cost-utility analysis consequences are combined into a single measure that combines quality of life outcomes with life expectancy outcomes (i.e. quality-adjusted life years or QALYs).

Our trial will therefore determine the effects on activity limitation and quality of life of participating in a rehabilitation program (supervised exercise, gait training and advice) after immobilisation for ankle fracture, and the economic consequences of doing so.

Prediction of outcome after ankle fracture is relatively imprecise. In our two trials evaluating components of rehabilitation after ankle fracture [7,8], performance-related variables (pain and dorsiflexion range of motion) soon after the period of immobilisation explained only 9 to 12% of the variance in activity limitation in the short- to medium-term [26]. Psychological variables (including pain catastrophising and depression) appear to be important predictors of outcome in people with other musculoskeletal conditions [27], but have not been examined after ankle fracture. This trial will therefore determine if psychological variables are stronger predictors of outcome than performance-related variables after ankle fracture.

Specific aims and objectives

1. To determine if rehabilitation intervention will reduce activity limitation and improve quality of life compared to advice intervention.
2. To determine if treatment effects are influenced by fracture severity and by the age and gender of participants
3. To assess the cost-effectiveness of rehabilitation compared to advice.
4. To determine the effects of rehabilitation on secondary outcomes: number of days to pain-free walking and return to full pre-fracture work, return to pre-fracture work and leisure activities, ankle range of motion, pain, walking speed, physical activity, and global perceived effect of treatment.
5. To establish predictors of outcome after ankle fracture.

Research plan – methods and techniques to be used

Experimental design and procedures

An assessor-blinded randomised controlled trial will be conducted. 342 participants will be randomly allocated into one of two groups: an advice group and a rehabilitation group - see Figure on page 4. Randomisation will be stratified by site (Royal North Shore Hospital, Royal Prince Alfred Hospital, Prince of Wales Hospital, Ryde Hospital, Blacktown Mount Druitt Hospital, Hornsby Ku-ring-gai Hospital and Mona Vale Hospital), blocking within strata (sites) using permuted random blocks. Randomisation will be concealed using a central randomisation service. Baseline measures will be obtained prior to randomisation. Outcomes will be determined at 1, 3 and 6 months. Health care costs will be estimated using standard methods and data on participants’ out-of-pocket costs will be collected at the 1, 3 and 6-month assessments.

Participants

Participants will be recruited from the fracture clinics in seven Sydney teaching hospitals (Royal North Shore Hospital, Royal Prince Alfred Hospital, Prince of Wales Hospital, Ryde Hospital, Blacktown Mount Druitt Hospital, Hornsby Ku-ring-gai Hospital and Mona Vale Hospital). All participants who fulfill the following criteria will be invited to participate:

1. ankle fracture treated with immobilisation (with or without surgical fixation)
2. immobilisation removed on the day of recruitment
3. approval received from orthopaedic specialist to weight-bear as tolerated or partial weight-bear
4. reduced ankle dorsiflexion range of motion (at least 30 mm less motion compared to the non-fractured leg using the weight-bearing lunge method) [28]
5. experiences at least 2 out of 10 pain in the ankle when up to 50% of body weight is borne through the affected leg
6. completed skeletal growth (i.e. no evidence of epiphyseal cartilage in the tibia in x-rays taken for fracture management)
7. no concurrent pathologies (e.g. symptomatic osteoarthritis, stroke, other fractures) which affect the ability to perform everyday tasks or the measurement procedures used in this study, and
8. provides informed consent.

Interventions

In this pragmatic randomised trial, the advice group will receive verbal and written advice about exercise at the time of cessation of immobilisation (a single session). The rehabilitation group will participate in a rehabilitation program, supervised by a physiotherapist, for one or two treatment sessions in the first week then one session per week for up to 3 weeks (advice intervention plus about five consultations). This is the usual frequency with which the treatments are delivered.

Participants in the advice group will be given advice in a single session in the fracture clinic, after cessation of immobilisation and after consultation with the treating orthopaedic specialist. A physiotherapist will instruct the participant to do exercises that focus on ankle movement in non-weight-bearing positions and will explain how to perform these exercises and how to progressively reduce the use of any walking aids at home. The participant will be given a handout that summarises this advice with text and figures.

Participants in the rehabilitation group will receive the advice intervention plus participate in a program that is designed, monitored and progressed by a physiotherapist. Three types of exercises will be prescribed - ankle mobility and strengthening exercises, stepping exercises, and exercises involving weight bearing and balancing on the affected leg. These exercises are routinely prescribed after immobilisation for ankle fracture and were used in our recently completed clinical trials evaluating the effects of passive stretch or manual therapy plus exercise after ankle fracture [7,8]. Exercise cards have been developed to standardise the exercises used between physiotherapists and between sites. In keeping with the pragmatic orientation of the trial, participating physiotherapists will not be prevented from administering stretches or manual therapy, but they will be informed of the findings of randomised trials investigating these interventions. Participants will receive gait training and ongoing advice about returning to their usual work and leisure activities. Participants will be encouraged to perform a carefully structured exercise program at home between
physiotherapy appointments, which they will record in an exercise diary.

Where it is deemed appropriate, participants in both groups will be instructed to use ice for pain relief and compression and elevation for management of swelling. A compression bandage (i.e. tubigrip) will be provided if required. Treatments will be administered by registered physiotherapists, who will be trained to provide the advice and rehabilitation interventions in accordance with the trial protocol.

Baseline measurements and measurement of outcomes

Outcome measurements will be made by an assessor who is blind to group allocation. In the baseline assessment, demographic and injury details will be recorded. Fracture severity will be rated according to the number of malleoli fractured [20] and the presence of dislocation, with unimalleolar fractures being classified as less severe and bi- or tri-malleolar fractures and any fractures with dislocation as more severe. Two psychological scales will also be assessed: depression, anxiety and stress will be measured using the Depression, Anxiety, Stress Scales 21-item version (DASS-21) [29], and pain catastrophising will be assessed using the Pain Catastrophising Scale [30].

Two primary outcomes and eight secondary outcomes will be assessed at baseline and at the three follow-up measurement sessions at 1, 3 and 6 months. One primary outcome is activity limitation assessed with the Lower Extremity Functional Scale and the second is quality-adjusted life years (QALY) measured by the Assessment of Quality of Life (AQoL) instrument. Secondary outcomes are the number of days to pain-free walking, the number of days to return to full pre-fracture work, return to pre-fracture work and leisure activities, ankle range of motion, pain, walking speed, physical activity, and the global perceived effect of treatment. We will also evaluate adherence, adverse events and participants’ perceptions of the credibility of interventions.

Primary outcomes

(1) Activity limitation: Activity limitation will be assessed using the Lower Extremity Functional Scale [9]. This involves the participant rating the degree of difficulty in performing 20 different functional activities on a 5-point scale ranging from 0 (‘extreme difficulty or unable to perform activity’) to 4 (‘no difficulty’). The scale has excellent test-retest reliability (intraclass correlation coefficient (ICC) 0.94), is more sensitive to change than other scales such as the SF-36 [9], and has high internal consistency and construct and concurrent validity for people with ankle fracture [31].

(2) Quality-adjusted life years: Utility will be measured at 6 months by the Assessment of Quality of Life (AQoL) instrument, which is designed to measure health-related quality of life and to be the descriptive system for a multi-attribute utility instrument. The AQoL measures five dimensions: illness, independent living, social relationships, physical senses and psychological well-being, all of which have been shown to be orthogonal and unidimensional. Developed by Australian researchers using state-of-the-art psychometric procedures, the AQoL has been shown to be internally consistent (alpha = 0.81) and to have a comparative fit index of 0.90 [32]. The AQoL has been shown to be reliable and is more sensitive to health status than other multi-attribute utility instruments [33].

Secondary outcomes

(1) Number of days to pain-free walking: All participants will be given a calendar on which to mark the first day they can walk pain-free for 10 metres at a comfortable pace. This will be used to calculate the number of days elapsed from the day of randomisation to pain-free walking [7].

(2) Number of days to return to full pre-fracture work: All participants who worked prior to fracture will be questioned about return to their pre-fracture work. This will be used to calculate the number of days elapsed from the day of randomisation to return to full pre-fracture work.

(3) Return to pre-fracture work and leisure: Percentage return to full pre-fracture work and leisure, where 0% is 'not participating at all' and 100% is 'returned to full level', will be measured at
baseline and the 1-, 3- and 6-month follow-up.

(4) **Ankle range of motion:** Ankle dorsiflexion range of motion will be measured using the weight-bearing lunge method [28] at baseline and at the 1-month follow-up.

(5) **Pain:** Pain on equal weight-bearing and on stair descent using a numerical rating scale (0 to 10), where 0 is ‘no pain’ and 10 is ‘worst pain you ever had’, will be measured at baseline and at the 1-, 3- and 6-month follow-up.

(6) **Walking speed:** Unaided walking speed will be measured over a 10 m distance using a stop watch at baseline and at the 1-month follow-up.

(7) **Level of physical activity:** Physical activity will be measured using the International Physical Activity Questionnaire - Short Form [34] at baseline and at the 1-, 3- and 6-month follow-ups. This is a valid and reliable questionnaire which will be used to calculate both the MET-minutes per week and to classify participants into three categories (low, moderate and high).

(8) **Global perceived effect of treatment:** Perceived effect of treatment will be measured on an 11-point scale from -5, ‘vastly worse’, to +5, ‘completely recovered’.

Participants will complete exercise diaries and physiotherapists will complete treatment logs. These will be analysed to ascertain adherence. Participants’ perceptions of the credibility of the interventions will be determined by questions administered at the 6-month follow-up. At the 6-month assessment, participants will also be asked open-ended questions about adverse events.

The 1, 3 and 6-month assessments will be performed on all randomised participants, in so far as this is possible, regardless of participants’ compliance with the experimental protocols.

**Economic evaluation**

The economic evaluation will consist of cost-effectiveness and cost-utility analyses. Costs will be measured in terms of direct costs to the health system and out-of-pocket costs to the participants over a 6-month period, and collected in a questionnaire at the 1, 3 and 6 month follow-up. From an economic perspective, costs are measured by resource use. This allows the identification of the opportunity cost of resources used, that is, what could have been achieved had those resources been allocated to the best alternative use. In this study the costs of the interventions and any out-of-pocket costs incurred by participants will be identified, measured and valued. The Table below indicates the type of resources which will be captured, the sources of data, and proposed methods of valuation.

<table>
<thead>
<tr>
<th>Type of Resource</th>
<th>Source of data</th>
<th>Method of valuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiotherapists’ time</td>
<td>Observation in the hospital settings</td>
<td>Salary rates plus on-costs for physiotherapists</td>
</tr>
<tr>
<td>Equipment</td>
<td>Survey of participants over 6 months</td>
<td>Manufacturer’s price (depreciated over 3 years)</td>
</tr>
<tr>
<td>Medication utilised or visits to general practitioners</td>
<td>Survey of participants over 6 months</td>
<td>Published prices (e.g. PBS and MBS reimbursement) and actual costs to participants</td>
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<tr>
<td>other healthcare professionals or practitioners in relation to the ankle fracture</td>
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The cost-effectiveness analysis will use our primary outcome measure, the Lower Extremity Functional Scale measure of activity limitation [9], as a measure of effectiveness. The cost-utility analysis will use the Assessment of Quality of Life (AQoL) instrument as a measure of utility. The analyses will examine differences between participants in the rehabilitation and advice groups in terms of costs incurred and reductions in perceived disability (cost-effectiveness analysis) or utility gained (cost-utility analysis).
The incremental cost-effectiveness (utility) ratio (ICER) will be calculated as:

\[ \text{ICER} = \frac{(C_R - C_A)}{(U_R - U_A)} \]

where C is average cost, U is the average effectiveness or utility score, and subscripts R and A denote the rehabilitation and advice arms. The rehabilitation program can be said to be cost-effective relative to advice about exercise if it (a) produces less activity limitation or greater utility at a lower cost or (b) the cost per activity limitation avoided or per QALY gained (i.e. the ICER) is less than some threshold value (e.g. $50,000).

Sensitivity analyses will be undertaken to explore the robustness and validity of the results. Both costs and outcomes will be varied in line with results from similar studies reported in the literature and the upper and lower limits of estimates from this study.

**Justification of a pragmatic trial design**

A pragmatic trial design [35,36] was chosen because the objective of this research is to help clinicians choose between two alternatives in the management of people with ankle fractures. Participants receiving the rehabilitation intervention will attend for rehabilitation and participants receiving the advice intervention will not, because the intent is to compare the effects of these two alternatives when they are administered as usually applied in the clinic. We will not match the number of treatment sessions for the advice group because, given the pragmatic orientation of the trial, it is more important to replicate current clinical practice. The pragmatic design means that the trial will provide information that will help clinicians decide if the provision of a rehabilitation program improves clinical outcomes. The results of the economic evaluation will only be meaningful if the trial design is pragmatic.

**Data quality**

Several strategies will be implemented in order to ensure data quality. All procedures will conform with The George Institute for International Health’s standard operating procedures for conduct of clinical trials. Assessors and treating physiotherapists will be adequately trained before they work on the trial. Compliance with the trial protocol will be closely monitored by an on-site Associate Investigator. Data forms and processing will be regularly scrutinised for accuracy and completeness. All data entry will be double-checked for accuracy. After the trial, the security of randomisation will be evaluated by comparing actual group allocations with a record of the randomisation schedule.

**Statistical analysis**

Analysis of the effects of intervention will be performed by CI Herbert with assistance from senior biostatisticians at The George Institute for International Health. Economic analyses will be performed by CI Haas with the assistance of CI Lin. Data will be coded to permit blinding to allocation in the statistical analysis.

To test the effects of intervention on continuous outcomes (activity limitation, quality of life, ankle range of motion, pain, global perceived effect of treatment), between-group comparisons will be conducted using longitudinal mixed models [37,38]. The independent variables will be a dummy-coded variable indicating group membership, the time at which the measurement was taken (four times, dummy-coded as three variables, with the baseline time as the referent category), and the three time by group interactions. The effect of rehabilitation at each of the three follow-up time points is estimated with the relevant interaction term. The model will incorporate random intercepts to account for the dependence of repeated measures. Survival analysis will be used to estimate between-group differences in days to pain-free walking and days to return to full pre-fracture work. Odds ratios will be calculated for physical activity and adverse events. The primary analysis will ignore stratification. Analysis will be by ‘intention-to-treat’ (i.e. all available data from all randomised participants will be analysed in the group to which the participant was allocated).

In a second analysis, designed to test the influence of fracture severity on treatment response, additional terms (fracture severity and the interactions of fracture severity with the group and time variables) will be entered into the model. The effect of fracture severity on treatment response will
be determined by examining the interactions between group membership, fracture severity and the
time variables.

A third analysis is designed to test the influence of participant age/gender on treatment response.
Participants will be divided into women aged over 50 and others. Again, additional terms
(age/gender and the interactions of age/gender with the group and time variables) will be entered
into the model. The effect of age/gender on treatment response will be determined by examining the
interactions between group membership, age/gender and the time variables.

The primary conclusions about effectiveness of rehabilitation will be based on between-group
comparisons of activity limitation and quality of life at 3 months. The primary conclusions about
whether fracture severity and age and gender influence the effectiveness of intervention will be
based on the interactions between these factors and rehabilitation at 3 months.

To test between-group differences in costs, two-tailed independent samples t-tests will be used and
bias-corrected bootstrapped estimates (1,000 replications) of the 95% confidence intervals for
between-group differences in mean costs will be obtained. Between-group differences in utilisation
will be tested using Fisher's exact test.

To establish the predictors of outcome after ankle fracture, univariate linear regression will be used
to examine the relationship between baseline variables (fracture severity, pain, ankle range of
motion, mobility, depression and pain catastrophising) predict activity limitation at 1-month and 6
months after removal of immobilisation. Significant variables (p ≤ 0.20) will then be examined with
a multivariate linear model.

Sample size calculation

As the interest in the primary analysis is on the effects of intervention at 3 months, rather than in a
global test of the effect of intervention over time, sample size requirements are simply those
required for the cross-sectional comparisons [37]. A sample of 76 participants (38 per group) would
provide an 80% probability of detecting a difference between the group means of 10 points on the
80-point Lower Extremity Functional Scale (assuming a SD of 15 points, based on data from our
recently completed trials [7,8]). This sample size will also provide 80% probability of detecting a
difference between the group means of 2.75 points on the 45-point Assessment of Quality of Life
scale (assuming a SD of 4 points, based on data from our recently completed trial [7,8]). Effects
smaller than these are unlikely to be considered clinically worthwhile. In our calculations we
assumed an alpha of 0.05, and we allowed for 5% loss to follow-up.

In order to power the trial for analyses of the interactions with fracture severity and age/gender of
participants, we need to recruit a larger sample. Simulations by Brookes and colleagues show that
the sample size inflation factor depends on the size of the interaction that is to be detected and the
subgroup ratio (i.e. the ratio of proportions of participants with and without the factor that identifies
the subgroup) [39]. The sample size needs to be inflated by a factor of 4.0 for the interaction [39],
and by a further factor of \((2 + k + 1/k)/4\), where \(k\) is the subgroup ratio [39]. We anticipate the
subgroup ratio for both severe:less severe fracture and women aged over 50:others is ~1:2 (based on
our recently completed studies [7,8]). Thus, to detect an interaction of the same magnitude as the
main effect with a subgroup ratio of 1:2, the inflation factor is approximately 4.5. Therefore, a
sample of \(72 \times 4.5 = 342\) participants (171 per group) will be recruited.

Outcomes and significance

Ankle fracture is a common injury. Rehabilitation programs are often provided to address the health
consequences (activity limitation and participation restriction) of the fracture and subsequent
immobilisation. There have been no randomised trials to evaluate the effects of a comprehensive
rehabilitation program after removal of immobilisation for ankle fracture.

We will conduct a definitive randomised controlled trial to determine the effects of a rehabilitation
program on activity limitation and quality of life. The results of this study will indicate if treatment
with a rehabilitation program produces clinically worthwhile effects for people following immobilisation for ankle fracture. In addition, the data may enable identification of groups who respond best to treatment. The findings will enable an evidence-based approach to the treatment of ankle fracture.

References


EXACT
EXercise or Advice after ankle fracture

STATISTICAL ANALYSIS PLAN

Version 4.0

30 July 2014
STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: EXACT

Title: EXercise or Advice after ankle fracTure

Authors:
Anne M Moseley, Paula R Beckenkamp, C Christine Lin, Marion Haas, Robert D Herbert

Principal Author of Analysis Plan: Robert D Herbert

Version: 4.0

Version date: 30 July 2013

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas. Laurent Billot also finds this plan to be in compliance with The George Institute’s SOP ST--SOP-04.

[Signature]
Robert Herbert
Chief Investigator

[Signature]
Anne Moseley
Principal Investigator

[Signature]
Laurent Billot
Statistics Division

30.7.2014
Date

30.7.14
Date

30. July 2014
Date
1 INTRODUCTION

The EXACT: EXercise or Advice after ankle fraCTure study is a randomised controlled trial comparing the effectiveness and cost-effectiveness of two common forms of treatment for ankle fracture: brief advice given at the time of removal of the immobilisation (Advice) and a formal physiotherapy rehabilitation program (Rehabilitation).

2 STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives are to:

2.1.1 Determine the effects of Rehabilitation compared to Advice on activity limitation and quality adjusted life years at 3 months.

2.1.2 Determine if these effects are influenced by two subgroups - fracture severity plus age and gender.

2.1.3 Evaluate the cost-effectiveness of Rehabilitation compared to Advice.

2.2 Secondary objectives

The secondary objectives are to:

2.2.1 Determine the effects of Rehabilitation compared to Advice on activity limitation and quality adjusted life years at 1 and 6 months.

2.2.2 Determine the effects of Rehabilitation compared to Advice on 17 secondary outcomes (number of days to pain-free walking, number of days to return to full pre-fracture work, return to pre-fracture work and leisure, ankle dorsiflexion range of motion, pain (during standing and stair descent), walking speed, physical activity (level and metabolic equivalents), global perceived effect of treatment, and health-related quality of life (total plus illness, independent living, social relationships, physical senses and psychological well-being domains)) at 1, 3 and 6 months.

2.2.3 Compare the safety of Rehabilitation compared to Advice at 6 months.

2.2.4 Identify predictors of outcome after ankle fracture.

3 STUDY DESIGN

3.1 Experimental design and procedures

The trial is a two-arm parallel-group randomised controlled trial in which participants will be randomly allocated into an Advice or Rehabilitation group after the immobilisation period that follows an ankle fracture. Allocation will be concealed, outcome assessment will be assessor-blinded and an intention-to-treat analysis will be used. A pragmatic approach will be taken to find out how effective the treatment is in clinical practice [1].

Concealed randomisation will occur after the completion of the baseline assessment. The randomisation sequence will be stratified by site, blocking within strata using permuted random blocks, and it will be concealed using a central telephone randomisation service provided by the NHMRC Clinical Trials Centre.

3.2 Study population

Participants will be recruited from the fracture clinics of seven public hospitals in Sydney, Australia: Royal North Shore Hospital, Royal Prince Alfred Hospital, Blacktown Mount Druitt
Hospital, Prince of Wales Hospital, Ryde Hospital, Hornsby Ku-ring-gai Hospital and Mona Vale Hospital. Royal North Shore Hospital, Prince of Wales Hospital and Royal Prince Alfred Hospital are major teaching hospitals with more than 500 beds. Ryde Hospital, Hornsby Ku-ring-gai Hospital and Mona Vale Hospital are smaller teaching hospitals with close to 200 beds. Blacktown Mount Druitt Hospital is two hospitals under the same administration. Blacktown Hospital is a large teaching hospital with approximately 400 beds, whereas Mount Druitt Hospital is smaller, with 200 beds. The fracture clinic for Blacktown Mount Druitt Hospital is conducted at Blacktown Hospital, but participants can be referred to either hospital to receive the study intervention.

The inclusion criteria are:

3.2.1 ankle fracture treated with immobilisation, with or without surgical fixation;
3.2.2 immobilisation removed on the day of recruitment;
3.2.3 approval received from the orthopaedic specialist to weight-bear as tolerated or partial weight-bear;
3.2.4 reduced ankle dorsiflexion range of motion (at least 30 mm less motion compared to the non-fracture ankle using the weight-bearing lunge method) [2];
3.2.5 at least 2 out of 10 pain in the ankle when up to 50% of body weight is borne through the affected leg;
3.2.6 completed skeletal growth (i.e. no evidence of epiphyseal cartilage in the tibia in x-rays taken for the fracture management);
3.2.7 no concurrent pathologies (e.g. symptomatic osteoarthritis, stroke, other fractures) which affect the ability to perform everyday tasks or the measurement procedures used in this trial; and
3.2.8 informed consent obtained.

3.3 Sample size

A sample of 76 participants (38 per group) would provide an 80% probability of detecting a difference between the group means of 10 points on the 80-point Lower Extremity Functional Scale (assuming a SD of 15 points, based on data from our previous trials [3, 4]). This sample size will also provide 80% probability of detecting a difference between the group means of 2.75 points on the 45-point Assessment of Quality of Life scale (assuming a SD of 4 points, based on data from our previous trial [3]). Effects smaller than these are unlikely to be considered clinically worthwhile. In our calculations we assumed an alpha of 0.05, and we allowed for 5% loss to follow up. We conservatively ignored the extra precision conferred by the longitudinal design.

In order to power the trial for the subgroup analyses of the interactions with fracture severity and age/gender of participants (primary objective 2.1.2) we need to inflate the sample size by a factor of \((k + 1)^2 / k\), where \(k\) is the sub-group ratio [5]. We anticipate the sub-group ratio for both severe:less severe fracture and women aged over 50:others is \(~1:2\) (based on our previous studies [3, 4]). Thus, a sample of 72 \(\times\) 4.5 = 342 participants (171 per group) will be randomised.

On 14 May 2013 a decision was made to terminate recruitment at the end of 2013 because of funding restrictions (end of NHMRC project grant funding).
4 INTERVENTIONS

Participants in the Advice group will be given advice in a single session in the fracture clinic, after removal of immobilisation and after consultation with the treating orthopaedic specialist. A registered physiotherapist will advise the participant to do exercises that involve ankle movement in non-weight-bearing positions and will explain how to perform these exercises and how to progressively reduce the use of walking aids. The participant will be given a handout that summarises this advice with text and figures.

Participants in the Rehabilitation group will receive the same advice but will also participate in an exercise program that is designed, monitored and progressed by a physiotherapist, with participants encouraged to perform a carefully structured exercise program at home. Three types of exercises will be prescribed: ankle mobility and strengthening exercises, stepping exercises, and exercises involving weight-bearing and balancing on the affected leg. These exercises are routinely prescribed after immobilisation for ankle fracture and were used in our previous trials [3, 4]. Exercise cards have been developed to standardise the exercises used. Participants will also receive gait training and ongoing advice about returning to usual work and leisure activities. In keeping with the pragmatic orientation of the trial, participating physiotherapists will not be prevented from administering other interventions. The rehabilitation program will be provided during two sessions in week one and in one session from weeks two to four; further consultations will be at the discretion of the physiotherapist. Participants will be discharged by their physiotherapist when they achieve their pre-fracture function, reach a plateau in their progress, or choose to discontinue the treatment.

5 OUTCOMES

Two primary outcomes and 17 secondary outcomes will be assessed at baseline and at three follow up measurement sessions at 1, 3 and 6 months, by an assessor blinded to group allocation. Adherence and participants’ perceptions of the credibility of interventions will also be evaluated. Data on participants’ out-of-pocket costs will be collected at 1, 3 and 6 months for the economic evaluation.

In the baseline assessment, demographic and injury details will be recorded. Fracture severity will be rated according to the number of malleoli fractured [6] and the presence of dislocation. Unimalleolar fractures will be classified as less severe and bi- or tri-malleolar fracture as more severe. The presence of dislocation, regardless of the number of malleoli fractured, will be classified as more severe. In addition, responses to two scales (Depression, Anxiety, Stress Scale [7] and the Pain Catastrophising Scale [8]) will be collected specifically for the prediction of outcome (secondary objective 2.2.4).

5.1 Primary outcomes

The primary outcomes are:

5.1.1 Activity limitation: will be measured using the 80-point Lower Extremity Functional Scale [9] which involves the participant rating the degree of difficulty in performing 20 functional activities on a 5-point scale ranging from 0 (‘extreme difficulty or unable to perform activity’) to 4 (‘no difficulty’).

5.1.2 Quality adjusted life years: will be measured using the Assessment of Quality of Life instrument, which is a multi-attribute utility instrument. It can also be used to measure health-related quality of life. The Assessment of Quality of Life measures five dimensions: illness, independent living, social relationships, physical senses and psychological well-being, all of which have been shown to be orthogonal and unidimensional [10].
5.2 Secondary outcomes

The secondary outcomes are:

5.2.1 **Number of days to pain-free walking**: participants will be given a calendar to mark the first day they can walk pain-free for 10 metres to calculate the number of days elapsed from the day of randomisation to pain-free walking [3].

5.2.2 **Number of days to return to full pre-fracture work**: participants who worked prior to fracture will be given a calendar to mark the first day they return to their pre-fracture work to calculate the number of days elapsed from the day of randomisation to return to full pre-fracture work.

5.2.3 **Return to pre-fracture work**: self-reported percentage return to full pre-fracture work, where 0% is ‘not participating at all’ and 100% is ‘returned to full level’.

5.2.4 **Return to pre-fracture leisure**: self-reported percentage return to full pre-fracture leisure, where 0% is ‘not participating at all’ and 100% is ‘returned to full level’.

5.2.5 **Ankle dorsiflexion range of motion**: measured using the weight-bearing lunge method at baseline and 1 month follow up [2].

5.2.6 **Pain during standing**: pain on equal weight-bearing will be measured using a numerical rating scale (0 to 10), where 0 is ‘no pain’ and 10 is ‘worst pain you ever had’, assessed at baseline and at the 1 month follow up.

5.2.7 **Pain during stair descent**: measured using a numerical rating scale (0 to 10), where 0 is ‘no pain’ and 10 is ‘worst pain you ever had’, assessed at baseline and at the 1 month follow up.

5.2.8 **Walking speed**: unaided walking speed over a 10 m distance will be measured using a stop watch at baseline and at the 1 month follow up.

5.2.9 **Physical activity (level)**: physical activity will be self-reported using the International Physical Activity Questionnaire-Short Form [11] and, based on their responses, participants will be classified into one of the three activity levels (low, moderate or high). Physical activity (level) will then be dichotomised as having low physical activity (yes/no).

5.2.10 **Physical activity (metabolic equivalent)**: the International Physical Activity Questionnaire-Short Form will also be used to calculate the metabolic equivalent minutes per week.

5.2.11 **Global perceived effect of treatment**: perceived effect of treatment will be measured on an 11-point scale from -5, ‘vastly worse’, to +5, ‘completely recovered’, assessed at 1, 3 and 6 months follow up.

5.2.12 **Health-related quality of life (total score)**: will be measured using the Assessment of Quality of Life instrument (0 to 45).

5.2.13 **Health-related quality of life illness domain**: will be measured using the Assessment of Quality of Life instrument items 1 to 3 (0 to 9).

5.2.14 **Health-related quality of life independent living domain**: will be measured using the Assessment of Quality of Life instrument items 4 to 6 (0 to 9).

5.2.15 **Health-related quality of life social relationships domain**: will be measured using the Assessment of Quality of Life instrument items 7 to 9 (0 to 9).

5.2.16 **Health-related quality of life physical senses domain**: will be measured using the Assessment of Quality of Life instrument items 10 to 12 (0 to 9).
5.2.17  Health-related quality of life psychological well-being domain: will be measured using the Assessment of Quality of Life instrument items 13 to 15 (0 to 9).

5.3 Safety

Safety will be evaluated using the number of adverse events reported by participants. At the 6 month follow up participants will be asked if they suffered any negative effects from the study treatment they received and, if they did, they will be asked to describe the negative effects.

5.4 Economic data

The economic evaluation will consist of cost-effectiveness and cost-utility analyses. Costs will be measured in terms of direct costs to the health system and out-of-pocket costs to the participants over a 6-month period. From an economic perspective, costs are measured by resource use. The costs of the interventions and any out-of-pocket costs incurred by participants will be identified, measured and valued. Economic data will be collected from participants at 1, 3 and 6 months follow up. The cost year will be 2013.

The types of resources that will be captured include:

5.4.1 Visits to hospital physiotherapist will be costed by physiotherapists’ time, estimated from their reports on the number of sessions provided to participants in the Rehabilitation group, based on salary rates plus on-costs for physiotherapists published by the NSW Health Service Health Professionals (State) Award (http://www.health.nsw.gov.au/careers/conditions/Awards/hsu_health_professional.pdf).

5.4.2 Visits to hospital or private physiotherapists recorded by participants will be used to calculate (1) transport and other costs for hospital physiotherapy for participants in the Rehabilitation group, (2) staff time (see section 5.4.1) plus transport and other costs for hospital physiotherapy for participants in the Advice group, and (3) consultation fees plus transport and other costs for private physiotherapy. Participants will record the number of visits to the physiotherapist (hospital or private), including information on out-of-pocket costs with charges, transport or any other costs involved. Transport and any other costs include travel (public transport, taxis, parking, tolls, motor vehicle use) and any other out-of-pocket costs incurred. The distance travelled to see the physiotherapist, recorded in kilometres, will be used to calculate motor vehicle expenses using the Australian Taxation Office rate for vehicles with a 1.601-2.6 litre engine capacity (74 cents per kilometre for the 2012 to 2013 financial year, https://www.ato.gov.au/Business/Deductions-for-business/Motor-vehicle-expenses/Calculating-your-deduction/Method-1---cents-per-kilometre/).

5.4.3 Equipment purchased by the participant will be evaluated based on the manufacturer’s price and/or actual costs to participants (depreciated over 3 years).

5.4.4 Visits to medical specialist, general practitioner, hospital emergency department and admission to hospital and medication details will be evaluated based on published prices (e.g. Pharmaceutical Benefits Schedule reimbursement) and/or actual costs to participants.

5.4.5 Visits to community services or alternative or complementary health practitioners will be evaluated based on actual costs to participants.
5.4.6 Participants will be asked the number of days away from paid work and the status of the leave, in the case of paid leave (e.g. sick leave, worker’s compensation, third party, etc). They will also record the number of days away from unpaid activities (e.g. study, voluntary work, household duties, leisure pursuits, etc). Both are assessed at 1, 3 and 6 months through a questionnaire. Days away from paid or unpaid activities will be reported as the number of days absent from work and or leisure activities as descriptive data.

The cost-effectiveness analysis will use the Lower Extremity Functional Scale as a measure of effectiveness. Thus, cost-effectiveness will be estimated as the incremental cost per unit reduction in activity limitation. The cost-utility analysis will use the Assessment of Quality of Life instrument as a measure of utility. We will capture survival by estimating the average survival of individuals using life tables. The incremental cost per quality adjusted life years gained will be calculated.

5.5 Process measures

Adherence will be assessed using an exercise calendar given to participants to record each day they complete the study exercises over the 6 month follow up period. The number of exercise days will be counted and expressed as a percentage of the number of days in the follow up period for each participant.

The treating physiotherapists will complete a form for each participant allocated into the Rehabilitation group which contains the following information: (a) number of treatment sessions scheduled, (b) number of treatment sessions attended, (c) date of discharge, (d) main reason for discharge, (e) specific exercises used, and (f) other treatments implemented. These data will be used to calculate the mean (standard deviation) number of treatment sessions attended, percentage of scheduled treatment sessions attended, and duration of rehabilitation (in days). An independent person will categorise the main reason for physiotherapy discharge. The frequency of prescription of each of the specific exercises will be calculated. The frequency of use of other treatments will be calculated, with an independent person categorising the types of treatment implemented.

The credibility of the intervention received will be assessed by a questionnaire at the 6 month follow up, where participants will report how satisfied they are with the study treatment they received. A 5-point Likert scale will be used: (1) extremely dissatisfied, (2) dissatisfied, (3) neutral, (4) satisfied, and (5) extremely satisfied.

An evaluation of the assessor blinding will be conducted at the end of the 1, 3 and 6 month follow ups. The assessor will record if he/she was unblinded (i.e. if they know the group allocation of the participant) and, if not, asked to guess the group allocation of the subject assessed. These data will be converted to a 4-point scale ((1) knows received Advice; (2) guesses received Advice; (3) guesses received Rehabilitation; (4) knows received Rehabilitation) to quantify the pattern of beliefs about group allocation in each group at the 1, 3 and 6 month follow-up assessments.

5.6 Data quality

To maintain data quality the following strategies will be implemented:

5.6.1 Assessors will ensure the completeness of the assessment forms by checking that all outcomes that have been correctly completed at the end of each assessment.

5.6.2 All data (all participants and all variables) will be double entered into an Excel spreadsheet.

5.6.3 Range checks will be performed for each variable.
5.6.4 To keep the assessors blinded, documents containing data that can reveal group allocation (such as calendars) will be stored in separate filing cabinets and the related data files will be password protected.

Once data from all participants have been obtained, the data will be imported into Stata. The data to be imported, including the variable names are defined in an Appendix for this Statistical Analysis Plan.

6 STATISTICAL ANALYSIS

6.1 General principles

All treatment evaluations will be conducted on the principle of intention-to-treat unless otherwise specified. Outcome data will be obtained from all randomised participants, in so far as this is possible, regardless of compliance with the trial protocol. Methods of handling missing data for the primary outcomes and endpoint are described in section 6.5. All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. Analysis will be adjusted for baseline values. No adjustment will be made for multiple testing for the three primary objectives. No adjustments for multiplicity are planned for the secondary objectives.

6.2 Blinding of subjects, therapists and assessors

Because of the nature of the intervention, it is not possible to blind participants and therapists. Our primary outcomes will be self-reported by participants and, therefore, cannot be truly assessor-blinded. However, the assessors who elicit primary outcome data and who collect secondary outcome data (some of which can be blinded, including ankle dorsiflexion range of motion and walking speed) will be unaware of group allocation.

6.3 Blind review

We will undertake a blind review after the data quality procedures have been completed (section 5.6) and prior to locking the database and finalising the SAP. The blind review will involve:

6.3.1 quantifying the amount and distribution of missing data in order to refine the handling of missing data (section 6.5)

6.3.2 evaluating the distribution of continuous variables

6.3.3 creating patient profile and mean plots for the primary outcomes versus time to determine if the data can be modelled as a simple function (e.g. linear, quadratic, exponential) in order to finalise the analysis of primary objectives 2.1.1 and 2.1.2 (see 6.6.1).

6.3.4 reviewing the negative effects reported by participants to establish categories for tabulation and analysis for secondary objective 2.2.3.

6.4 Blind analysis

The person(s) responsible for developing this SAP will not be unblinded until after the SAP has been fully signed off. Furthermore, the statistical analysis will be conducted by a statistician who will be blinded to group allocation by dummy coding the group names. The results will be unblinded to the rest of the team once the final statistical report has been completed.

6.5 Missing data handling

It is anticipated that missing data will be ‘Missing At Random’ (i.e. missing randomly, conditional on measured covariates). After considering the amount and distribution of missing data (section 6.3.1), the likely approach will be to use multiple imputation to impute missing data for the primary outcomes (activity limitation and quality adjusted life years) [12]. All baseline
data will be used for the imputation. We do not plan to impute missing data for any of the secondary outcomes or secondary endpoints.

6.6 Statistical analysis

6.6.1 Determine the effects of Rehabilitation compared to Advice on activity limitation and quality adjusted life years at 3 months (primary objective 2.1.1)

To test the effects of intervention on activity limitation and quality adjusted life years, between-group comparisons will be conducted using longitudinal mixed models [13, 14]. It is anticipated that these outcomes will be normally distributed. If the blind review (6.3.3) suggests that individual participants’ recovery profiles follow a consistent and easily modelled pattern, time will be treated as a continuous variable subject to the appropriate transformations. Alternatively, if recovery profiles are highly variable in shape or not easily modelled with a simple function, time will be treated as a dummy-coded categorical variable (using baseline values as a fixed covariate and looking at group x time interactions). The effect of Rehabilitation at a particular time will be estimated from the relevant group by time interaction. The model will incorporate random intercepts to account for the dependence of repeated measures. The primary conclusions about effectiveness of Rehabilitation will be based on between-group comparisons of activity limitation and quality adjusted life years at 3 months.

6.6.2 Determine if these effects are influenced by two subgroups - fracture severity plus age and gender (primary objective 2.1.2)

Two subgroup analyses are planned a priori. The first investigates the influence of fracture severity on the treatment effects. For this analysis unimalleolar fracture without dislocation will be considered as ‘less severe’ and unimalleolar fracture with dislocation or bi- or tri-malleolar fracture as ‘more severe’. The second subgroup analysis investigates the influence of age and gender on the treatment effects. For this analysis participants will be divided into ‘women aged over 50 years’ and ‘others’ (i.e. all men and women aged 50 years or lower).

In the analysis designed to test the influence of fracture severity on treatment response, additional terms (fracture severity and the interactions of fracture severity with the group and time variables) will be entered into the longitudinal mixed model. The effect of fracture severity on treatment response will be determined by examining the interactions between group membership, fracture severity and the time variables. The primary conclusions about whether fracture severity influences the effectiveness of intervention will be based on the interactions between this factor and effects of Rehabilitation for activity limitation and quality adjusted life years at 3 months.

A similar analysis will test the influence of participant age and gender on treatment response. Participants will be divided into women aged over 50 and others. Again, additional terms (age/gender and the interactions of age/gender with the group and time variables) will be entered into the model. The effect of age/gender on treatment response will be determined by examining the interactions between group membership, age/gender and the time variables. The primary conclusions about whether age and gender influence the effectiveness of intervention will be based on the interactions between these factors and effects of Rehabilitation for activity limitation and quality adjusted life years at 3 months.

6.6.3 Evaluate the cost-effectiveness of Rehabilitation compared to Advice (primary objective 2.1.3)

If there is a statistically significant difference between groups in the primary outcomes, we will conduct an economic evaluation to examine differences between participants in
the Rehabilitation and Advice groups in terms of costs incurred and changes in perceived activity limitation (cost-effectiveness analysis) or quality adjusted life years (utility) gained (cost-utility analysis). The incremental cost-effectiveness (utility) ratio (ICER) will be calculated as: ICER = (C_R – C_A)/(U_R – U_A), where C is average cost, U is the average effectiveness or utility score, and subscripts R and A denote the Rehabilitation and Advice arms. The Rehabilitation program can be said to be cost-effective relative to Advice about exercise if it (a) produces less activity limitation or greater utility at a lower cost or (b) the cost per activity limitation avoided or per quality adjusted life years gained (i.e. the incremental cost-effectiveness (utility) ratio) is less than some threshold value ($50,000 to $70,000 per quality adjusted life years gained). Cost-effectiveness ratios will be estimated using bootstrapping techniques (1,000 replications) and presented graphically on cost-effectiveness planes. Acceptability curves will also be estimated. Bias-corrected bootstrapped estimates (1,000 replications) will be used to test for the difference in mean costs and to obtain 95% confidence intervals for between-group differences in mean costs. Between-group differences in utilisation will be tested using Fisher’s exact test. Sensitivity analyses will be undertaken to explore the robustness and validity of the results. Both costs and outcomes will be varied in line with results from similar studies reported in the literature and the upper and lower limits of estimates from this trial.

6.6.4 Determine the effects of Rehabilitation compared to Advice on activity limitation and quality adjusted life yearshealth-related quality of life at 1 and 6 months (secondary objective 2.2.1)

To test the effects of intervention on activity limitation and quality adjusted life years at 1 and 6 months, between-group comparisons will be conducted using longitudinal mixed models, see section 6.6.1.

6.6.5 Determine the effects of Rehabilitation compared to Advice on 17 secondary outcomes at 1, 3 and 6 months (secondary objective 2.2.2)

Fourteen of the secondary outcomes are continuous variables (return to pre-fracture work and leisure, ankle dorsiflexion range of motion, pain during standing and during stair descent, walking speed, physical activity metabolic equivalents, global perceived effect of treatment, health-related quality of life (total plus illness, independent living, social relationships, physical senses and psychological well-being domains)). To test the effects of intervention on these continuous outcomes between-group comparisons will be conducted using longitudinal mixed models (see 6.6.1).

Two of the secondary outcomes are time to events (number of days to pain-free walking, number of days to return to full pre-fracture work). Survival analysis will be used to estimate between-group differences in these variables. Survival curves will be constructed on the basis of the dates participants returned to full pre-fracture work and could walk pain-free for 10m. Participants with incomplete follow-up data or who do not return to full-work or pain-free walking at the time of their last follow-up will be censored. We will use the log-rank test and Kaplan-Meier survival probability estimates to describe both return to pain-free walking and full pre-fracture work. The effect of intervention will be quantified with the hazard ratio. If the proportional hazards assumption is satisfied, survival of the two groups will be compared using Cox regression. If the proportional hazards assumption is violated, survival of the two groups will be compared using the log-rank test. If at least 50% of the sample return to pain-free walking or full pre-fracture work the median survival times for each group will be reported.
One of the secondary outcomes is categorical data (physical activity level). The ratio of the odds of being classified as having ‘low’ physical activity will be estimated at 1, 3 and 6 months using mixed effects logistic regression models.

6.6.6 Compare the safety of Rehabilitation compared to Advice at 6 months (secondary objective 2.2.3)

During the blind review phase, an independent person will group the negative effects into categories. The categories will be finalised during the blind review phase, but are likely to include pain or discomfort (during exercise or daily activities) and delayed fracture healing. The number of participants with each category of negative effects in each group will be reported. The relative risk for reporting a negative effect during the 6 month follow up will be evaluated using Fisher’s exact test or a chi-squared test.

6.6.7 Identify predictors of outcome after ankle fracture (secondary objective 2.2.4)

To establish the predictors of outcome after ankle fracture we will use baseline variables selected a priori (including fracture severity, pain, ankle range of motion, mobility, depression, anxiety and stress, and pain catastrophising) to predict activity limitation at 1-month and 6 months after removal of immobilisation. A multivariate prediction model will be developed using methods described by Steyerberg [15]. A separate protocol will be developed for this objective.

6.7 Adjusting for multiple comparisons

P-values will not be adjusted for multiplicity as outcomes and time points are clearly categorised by degree of importance (primary and secondary).

7 REPORTING DATA

A CONSORT diagram will be used to report the number of people with ankle fracture screened, the reasons for exclusion, the total number of participants randomised into the Advice and Rehabilitation groups, and the number of participants lost to follow up at each assessment point (see Figure 1, page 15).

Summaries of continuous variables which are normally distributed will be presented as means and standard deviations. Skewed continuous variables will be presented as medians and inter-quartile ranges. Categorical variables will be presented as frequencies and percentages. Table shells are shown in section 9.

It is expected that this trial will generate at least two papers for submission to peer-reviewed journals. The first paper will focus on the effectiveness and cost-effectiveness analyses (primary objectives 2.1.1, 2.1.2 and 2.1.3, plus secondary objectives 2.2.1, 2.2.2, and 2.2.3). The baseline data for this paper is shown in Table 1 (page 16), the primary and secondary outcomes are presented in Tables 2 and 3 (pages 17-18), respectively, the process measures are presented in Table 4 (page 19), and the economic data are presented in Tables 5 (page 20) and 6 (page 21). The second paper will focus on the predictors of outcome analysis (secondary objective 2.2.4).
8 REFERENCES


9 FIGURES AND TABLES
Figure 1. Study flow-chart.

Assessed for eligibility (n = xxxx)

Excluded (n = xxx)
1. Fracture not treated with immobilisation (n = xxx)
2. Immobilisation not removed on the day of recruitment (n = xxx)
3. Unable to weight-bear as tolerated or partial weight-bear (n = xxx)
4. No reduced ankle dorsiflexion range of movement (n = xxx)
5. Less than 2 out of 10 pain (n = xxx)
6. Incomplete skeletal growth (n = xxx)
7. Concurrent pathologies (n = xxx)
8. No informed consent (n = xxx)

Randomised (n = xxx)

Advice group (n = xxx)
Received Advice (n = xxx)
Received Rehabilitation (n = xxx)
Did not receive Advice or Rehabilitation (n = xxx)
Received extra physiotherapy (n = xxx)

Rehabilitation group (n = xxx)
Received Advice (n = xxx)
Received Rehabilitation (n = xxx)
Did not receive Advice or Rehabilitation (n = xxx)
Received extra physiotherapy (n = xxx)

Enrolment

Allocation

1 month follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

1 month follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

3 months follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

3 months follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

6 months follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

6 months follow up
Lost to follow up (give reasons) (n = xx)
Total analysed (n = xxx)

Follow up and Analysis
Table 1. Baseline characteristics of the study participants. Continuous variables are presented as means (SD) and categorical as frequency counts (%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice group (n=xxx)</th>
<th>Rehabilitation group (n=xxx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>female</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Age at fracture, years</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Ankle fractured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>right</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Cause of fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>road traffic accident (pedestrian or bicycle)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>road traffic accident (car or motorbike)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>fall</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>sporting injury</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>other</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Fracture severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>less severe*</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>more severe*</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Open reduction and internal fixation</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Length of immobilisation, days</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Type of immobilisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>backslab</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>cast</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>brace</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Lower Extremity Functional Scale (0-80)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Quality adjusted life years (0-1)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Quality of life (0-45)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Health-related quality of life - - illness domain (0-9)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Health-related quality of life - - independent living domain (0-9)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Health-related quality of life - - social relationships domain (0-9)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Health-related quality of life - - physical senses domain (0-9)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Health-related quality of life - - psychological well-being domain (0-9)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Return to pre-fracture work (0-100%)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Return to pre-fracture sport/leisure/recreation (0-100%)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>International Physical Activity Questionnaire, MET min/week</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>International Physical Activity Questionnaire, activity low</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>moderate or high</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Pain standing with equal weight on both legs, (0-10)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Pain walking down stairs, (0-10)**</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
</tr>
<tr>
<td>Statistic</td>
<td>Mean ± Standard Deviation</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Unaided walking speed, m/sec</strong></td>
<td>xx.x (xx.x) xx.x (xx.x)</td>
<td></td>
</tr>
<tr>
<td><strong>Ankle dorsiflexion range of motion, mm</strong></td>
<td>xx.x (xx.x) xx.x (xx.x)</td>
<td></td>
</tr>
</tbody>
</table>

*Less severe = 1 malleoli fractured; more severe = 2 or 3 malleoli fractured [6] or the presence of dislocation regardless of the number of malleoli fractured. **As per the weight-bearing lunge method (-) values represent the distance between the knee and the wall; (+) values represent the distance between the great toe and the wall [2]. MET = metabolic equivalents.
Table 2. Primary outcomes presented as means (SD) and the mean between-group difference (95% confidence interval) for the Advice and Rehabilitation (Rehab) groups at 1, 3 and 6 months.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice 1 month (n=xxx)</th>
<th>Rehab 1 month (n=xxx)</th>
<th>Difference 1 month</th>
<th>Advice 3 months (n=xxx)</th>
<th>Rehab 3 months (n=xxx)</th>
<th>Difference 3 months</th>
<th>Advice 6 months (n=xxx)</th>
<th>Rehab 6 months (n=xxx)</th>
<th>Difference 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower Extremity Functional Scale (0-80)</strong></td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td><strong>Quality adjusted life years (0-1)</strong></td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
</tbody>
</table>

* p < 0.05
Table 3. Secondary outcomes. Continuous variables are presented as means (SD) and mean between-group difference (95% confidence interval). Categorical variables are presented as frequency counts (%) and odds ratio (95% confidence interval).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice 1 month (n=xxx)</th>
<th>Advice 3 months (n=xxx)</th>
<th>Difference 3 months (n=xxx)</th>
<th>Rehab 1 month (n=xxx)</th>
<th>Rehab 3 months (n=xxx)</th>
<th>Difference 3 months (n=xxx)</th>
<th>Difference 6 months (n=xxx)</th>
<th>Difference 6 months (n=xxx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to pre-fracture work (0-100%)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Return to pre-fracture sport/leisure/recreation (0-100%)</td>
<td>(xx.x)</td>
<td>(xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x)</td>
<td>(xx.x - xx.x)</td>
<td>(xx.x)</td>
<td>(xx.x - xx.x)</td>
</tr>
<tr>
<td>International Physical Activity Questionnaire, MET min/week</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>International Physical Activity Questionnaire, low moderate or high</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Pain standing with equal weight on both legs (0-10)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Pain walking down stairs (0-10)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Unaided walking speed, m/sec</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ankle dorsiflexion range of motion, mm (-5 to +5)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Global perceived effect of treatment (0-45)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Health-related quality of life (0-45)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Health-related quality of life - illness domain (0-9)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Health-related quality of life - independent living domain (0-9)</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Health-related quality of life - -</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>social relationships domain (0-9)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health-related quality of life - -</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
</tr>
</thead>
<tbody>
<tr>
<td>physical senses domain (0-9)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health-related quality of life - -</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
<th>XX.X</th>
</tr>
</thead>
<tbody>
<tr>
<td>psychological well-being domain (0-9)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X - XX.X)</td>
<td>(XX.X)</td>
<td>(XX.X)</td>
</tr>
</tbody>
</table>

As per the weight-bearing lunge method (-) values represent the distance between the knee and the wall; (+) values represent the distance between the great toe and the wall [2]; NA=not assessed at this time point. MET = metabolic equivalents.
Table 4. Process measures. Continuous variables are presented as means (SD) and categorical as frequency counts (%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice group (n=xxx)</th>
<th>Rehabilitation group (n=xxx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of study days on which study exercises were performed</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
</tr>
<tr>
<td>Duration of rehabilitation (days)</td>
<td>NA</td>
<td>xx.x (xx)</td>
</tr>
<tr>
<td>Reason for discharge from rehabilitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Y</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Z</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Number of physiotherapy sessions attended</td>
<td>NA</td>
<td>xx.x (xx)</td>
</tr>
<tr>
<td>Percentage of scheduled physiotherapy sessions attended</td>
<td>NA</td>
<td>xx.x (xx)</td>
</tr>
<tr>
<td>Exercises used in rehabilitation program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A : 1B : 1C : 1D : 1E</td>
<td>NA</td>
<td>n (%) : n (%) : n (%) : n (%) : n (%)</td>
</tr>
<tr>
<td>2A : 2B : 2C : 2D : 2E</td>
<td>NA</td>
<td>n (%) : n (%) : n (%) : n (%) : n (%)</td>
</tr>
<tr>
<td>3A : 3B : 3C : 3D : 3E</td>
<td>NA</td>
<td>n (%) : n (%) : n (%) : n (%) : n (%)</td>
</tr>
<tr>
<td>Implemented other exercises</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>X</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Y</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Z</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Implemented passive stretches</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>X</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Y</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Z</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Implemented manual therapy</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>X</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Y</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Z</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Implemented other interventions</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>X</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Y</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Z</td>
<td>NA</td>
<td>n (%)</td>
</tr>
<tr>
<td>Assessor beliefs about group allocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>knows Advice : guesses Advice : guesses Rehabilitation : knows Rehabilitation</td>
<td>n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%) : n (%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Health service resource use: mean (SD) resource use per participant or the proportion of participants using a type of resource (%), between-group differences (mean, 95% CI) and unit cost per resource use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice group (n=xxx)</th>
<th>Rehabilitation group (n=xxx)</th>
<th>Between-group difference</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consultations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital physiotherapist</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>43.80/hour¹</td>
</tr>
<tr>
<td>Private physiotherapist</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>Actual costs as reported by participants</td>
</tr>
<tr>
<td>Medical specialist</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>75.50/visit²</td>
</tr>
<tr>
<td>General practitioner</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>36.30/visit²</td>
</tr>
<tr>
<td>Alternative health services</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>Actual costs as reported by participants</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department visit</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>347.75/visit³</td>
</tr>
<tr>
<td>Admission</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>7,630.11/separation⁴</td>
</tr>
<tr>
<td><strong>Prescription medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of participants using</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>Various⁵</td>
</tr>
<tr>
<td><strong>Other resources</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of participants using</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx - xx.x)</td>
<td>Actual costs as reported by participants</td>
</tr>
<tr>
<td>resources not captured above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources of valuation:
Table 6. Direct cost to the healthcare system, out-of-pocket cost, and total cost: mean (SD) costs per group and mean (95%CI) between-group differences

<table>
<thead>
<tr>
<th>Variables</th>
<th>Advice group (n=xxx)</th>
<th>Rehabilitation group (n=xxx)</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cost to healthcare system¹</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td>Out-of-pocket cost²</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
<tr>
<td>Total</td>
<td>xx.x (xx)</td>
<td>xx.x (xx)</td>
<td>xx.x (xx.x - xx.x)</td>
</tr>
</tbody>
</table>

¹Includes costs of hospital physiotherapists, medical specialists, general practitioners, emergency department visits, hospital admissions and prescription medications.

²Includes gap and/or transport or use of private vehicle costs accompanying direct cost to the healthcare system, plus treatment and/or transport or use of private vehicle costs to private physiotherapists, alternative health services and other resources. Transport costs are valued as actual costs as reported by participants, private vehicle costs are valued at AU$0.74 per kilometre travelled, according to the rate of a medium-sized vehicle for work-related kilometre published by the Australian Taxation Office.
eAppendix

EXACT Intervention Guidelines for Physiotherapists Providing Intervention for Participants in the Advice and Rehabilitation Groups

Advice Sheet Provided for Participants Allocated to Both Advice and Rehabilitation Groups

Exercises Implemented for Participants Allocated to Rehabilitation Group
EXACT intervention guidelines

BOTH REHABILITATION GROUP AND ADVICE GROUP

Both groups will receive the "Exercise and advice for ankle fracture" handout in the fracture clinic.

REHABILITATION GROUP

The focus of treatment for the REHABILITATION group is exercise. Three categories of exercises will be prescribed, one exercise from each of the following categories:
1. ankle mobility and strengthening exercises (light resistance exercises progressing to hopping exercises)
2. stepping exercises (stepping forward/backward with the unaffected leg on a level surface progressing to stepping down), and
3. weight bearing and balancing on the affected leg (maximum weight bearing in 2-legged stance progressing to the lateral weight bearing exercise)

The exercise stage (ie, A to E) and the degree of difficulty within each stage will be selected so that participants can only just complete 10 repetitions at a time. Using exercise 3 as an example, initially participants may not be able to fully weight bear on their leg because of pain. Exercise 3-A would be selected, with the target set at the weight that the participant can achieve 10 times only before needing a break. This target weight would then be increased until the participant can fully weight bear. The participant would then progress to exercise 3-B, until they can stand on 1-leg for 10 lots of 5 seconds. They would then progress to exercise 3-C, and so on.

The treating physiotherapist will determine the stage of each exercise and the degree of difficulty within each stage, and progress the exercises for each participant. It is okay to 'skip' stages (eg, start on stage 1-B if the participant can do heel raises in standing in the initial assessment), but the participant should complete one of the exercises in each category.

Participants will complete 3 sets of 10 repetitions per exercise category every day. Exercise 1-A is an exception as this involves 10 repetitions each of 4 different theraband exercises (ie, 40 repetitions in total).

<table>
<thead>
<tr>
<th>Progression</th>
<th>Exercise category 1</th>
<th>Exercise category 2</th>
<th>Exercise category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Theraband exercises</td>
<td>Stepping forward &amp; backward</td>
<td>Taking as much weight on your leg as possible</td>
</tr>
<tr>
<td>B</td>
<td>Heel raises standing on both feet</td>
<td>Step ups</td>
<td>Standing on 1 leg</td>
</tr>
<tr>
<td>C</td>
<td>Heel raises standing with foot on a chair</td>
<td>Lunges to a wall</td>
<td>Standing on 1 leg on a piece of foam</td>
</tr>
<tr>
<td>D</td>
<td>Heel raises standing on 1 foot</td>
<td>Stepping exercise</td>
<td>Standing on 1 leg on a piece of foam with your eyes shut</td>
</tr>
<tr>
<td>E</td>
<td>Heel raises standing on 1 foot on a step</td>
<td>Step downs</td>
<td>Standing on 1 leg throwing a ball</td>
</tr>
</tbody>
</table>

Other treatments which CAN be implemented
- treatment(s) to decrease swelling
  - compression with tubigrip
  - elevation with ankle motion
- treatment to decrease pain (eg, after exercise)
  - ice packs
  - general advise on pacing for exercise and activity
- progression of walking aids
- advise about gait
- advice about returning to usual activities
- skin and scar care
- manual therapy and passive stretch

Treatments which CANNOT be implemented
- EPAs other than ice packs (eg, interferential, ultrasound)
- ankle taping
- exercises other than those described in the exercise sheets (eg, wobble board exercises)
- orthotics

The number of sessions is not mandated by the trial protocol (suggested framework is 2 sessions in week 1 then 1 session per week in weeks 2 to 4). The timing of discharge is not mandated by the trial protocol.
Exercise and advice for ankle fracture

Exercise
(1) trace the alphabet with your foot

- Trace letters of the alphabet one after another in the air with your foot, keeping your knee still
- This picture is an example of tracing the letter A with your foot

- Move your foot in each direction as far as you can go
- Progress the exercise by tracing larger letters requiring larger ankle movements
- Trace 30 letters, twice a day
- Exercise in a comfortable chair with your knee straight and your leg resting on a second chair, coffee table or foot rest. Allow your foot to dangle over the edge
- You may feel some discomfort in your ankle which should settle quickly after the exercise is completed

(2) ankle up/down and in/out movements

- Pull your foot towards you then point your toes
- Turn your foot inward and then outwards keeping your knee still

- Move your foot in each direction as far as you can go
- Progress the exercises by using larger ankle movements
- Do 30 repetitions of each movement, twice a day

Advice

- You may experience swelling. Reduce this by:
  - wearing the piece of tubigrip provided by your physiotherapist
  - elevating your foot and ankle (including while doing ankle exercise)

- You may experience some pain as you start moving again. Reduce this by:
  - applying ice packs
  - pacing your exercise and activity (have rest breaks and distribute throughout the day)

- Walking:
  - gradually increase the weight borne through your leg (reducing support from crutches)
  - try and place your heel on the ground first at the start of each step
  - take equal step lengths for both legs
  - gradually increase walking distance

- Return to daily activities and sport:
  - gradually increase the amount of activity
  - no contact sports until you get approval from your orthopaedic doctor

- You may experience some swelling and pain in the ankle over the next 6 months as you increase your level of activity back to pre-fracture levels, this is a normal part of recovery.
**Ankle twisting outwards exercise**

Tie the rubber band to something heavy.

Place a loop of the rubber band over your left foot.

Slide sideways until the rubber band is stretched slightly and your foot is turned inwards.

Slowly turn your left foot outward against the resistance of the rubber band. Keep your knee pointed towards the ceiling at all times.

Return to the starting position. Relax then repeat.

Do 10 repetitions every day.

**Ankle twisting inwards exercise**

Tie the rubber band to something heavy.

Place a loop of the rubber band over your left foot.

Slide sideways until the rubber band is stretched slightly and your foot is turned outwards.

Slowly turn your foot inwards against the resistance of the rubber band. Keep your knee pointed towards the ceiling at all times.

Return to the starting position. Relax then repeat.

Do 10 repetitions every day.

**Ankle bending exercise**

Tie the rubber band to something heavy.

Place a loop of the rubber band around the ball of your left foot. Slide back so that your toe is pointed when the rubber is stretched slightly.

Slowly pull your toes towards your head against the resistance of the rubber band.

Return to the starting position. Relax then repeat.

Do 10 repetitions every day.

**Ankle pointing exercise**

Put the rubber band around the ball of your left foot and pull back until the rubber is stretched slightly.

Slowly point your toes against the resistance of the rubber band.

Return to the starting position. Relax then repeat.

Do 10 repetitions every day.
Ankle twisting outwards exercise  
(1A-right)

Tie the rubber band to something heavy.  
Place a loop of the rubber band over your right foot.  
Slide sideways until the rubber band is stretched slightly and your foot is turned inwards.  

Slowly turn your right foot outward against the resistance of the rubber band. Keep your knee pointed towards the ceiling at all times.  
Return to the starting position. Relax then repeat.  
Do 10 repetitions every day.

Ankle twisting inwards exercise  
(1A-right)

Tie the rubber band to something heavy.  
Place a loop of the rubber band over your right foot.  
Slide sideways until the rubber band is stretched slightly and your foot is turned outwards.  

Slowly turn your foot inwards against the resistance of the rubber band. Keep your knee pointed towards the ceiling at all times.  
Return to the starting position. Relax then repeat.  
Do 10 repetitions every day.

Ankle bending exercise  
(1A-right)

Tie the rubber band to something heavy.  
Place a loop of the rubber band around the ball of your right foot. Slide back so that your toe is pointed when the rubber is stretched slightly.  

Slowly pull your toes towards your head against the resistance of the rubber band.  
Return to the starting position. Relax then repeat.  
Do 10 repetitions every day.

Ankle pointing exercise  
(1A-right)

Put the rubber band around the ball of your right foot and pull back until the rubber is stretched slightly.  

Slowly point your toes against the resistance of the rubber band.  
Return to the starting position. Relax then repeat.  
Do 10 repetitions every day.
Heel raises standing on both feet

1. Stand with equal weight on both feet.
2. Lift heels to stand on the balls of your feet.
3. Return to the starting position. Relax and repeat.
4. Do 3 sets of 10 repetitions every day.

Heel raises standing with foot on a chair

1. Stand with your affected foot on the ground. Put your opposite foot on a chair in front of you.
2. Put as much weight through the foot on the ground as possible.
3. Lift heel to stand on the ball of your foot.
4. Return to the starting position. Relax and repeat.
5. Do 3 sets of 10 repetitions every day.

Heel raises standing on 1 foot

1. Stand on your affected leg.
2. If required, rest your hand on the wall to keep your balance.
3. Lift heel to stand on the ball of your foot.
4. Return to the starting position. Relax and repeat.
5. Do 3 sets of 10 repetitions every day.

Heel raises standing on 1 foot on a step

1. Stand with the ball of your affected foot on a step or wooden block and lower your heel towards the floor.
2. If required, rest your hand on the wall to keep your balance.
3. Lift heel to stand on the ball of your foot.
4. Return to the starting position. Relax and repeat.
5. Do 3 sets of 10 repetitions every day.
**Stepping forward and backward** (2A)

Stand on your affected leg. Keep the foot flat on the ground at all times.

If required, rest your hand on the wall to keep your balance.

Step forwards and backwards with your other leg. Relax and repeat.

Do 3 sets of 10 repetitions every day.

**Step ups** (2B)

Place your affected foot on a step or wooden block.

Step up and then back down with your other leg. Relax and repeat.

Step height =

Do 3 sets of 10 repetitions every day.

**Lunges to a wall** (2C)

Stand with your affected foot pointing straight toward a wall, with your hands resting gently on the wall.

Bend at your ankle and move your knee toward the wall. Keep your heel is in contact with the ground at all times.

Return to the starting position. Relax and repeat.

Distance between toes and wall =

Do 3 sets of 10 repetitions every day.

**Stepping exercise** (2D)

Stand with your affected foot on a step or wooden block. Raise the ball of your other foot off the ground so only your heel is in contact with the ground.

Slowly straighten your affected leg fully so that your other foot lifts off the ground. If required, rest your hand on the wall to keep your balance.

Slowly bend your affected leg so that your other heel touches the ground gently.

Step height =

Do 3 sets of 10 repetitions every day.
Step downs

Stand on a step or wooden block.
Step forward off the step to gently touch your unaffected heel on the ground. Keep your affected foot flat on the step at all times.
Step back up onto the step. Relax and repeat.

Step height =
Do 3 sets of 10 repetitions every day.

Taking as much weight on your leg as possible

Stand with your affected foot on bathroom scales and your other foot on a telephone book (so both feet are level). Try and hold this position for 5 seconds.

Take as much weight on your affected leg as possible.

Target weight =
Take the weight off your leg. Relax and repeat.
Do 3 sets of 10 repetitions every day.

Standing on 1 leg

Stand on your affected leg without holding onto anything. Try and hold this position for 5 seconds.

Stand on both feet. Relax and repeat.
Do 3 sets of 10 repetitions every day.

Standing on 1 leg on a piece of foam

Stand on your affected leg on a piece of foam without holding on to anything. Try and hold this position for 5 seconds.

Stand on both feet. Relax and repeat.
Do 3 sets of 10 repetitions every day.
Standing on 1 leg on a piece of foam with your eyes shut

Stand on your affected leg on a piece of foam without holding on to anything. Try and hold this position for 5 seconds with your eyes shut.

Stand on both feet. Relax and repeat.

Do 3 sets of 10 repetitions every day.

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Standing on 1 leg throwing a ball

Stand on your affected leg whilst throwing a ball against a wall.

Stand on both feet. Relax and repeat.

Gradually increase the number of throws without touching your foot to the ground.

Do 3 sets of 10 repetitions every day.