THE GEORGE INSTITUTE
for Global Health

EXACT
EXercise or Advice after ankle fracture

STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: EXACT

Title: EXercise or Advice after ankle fraCTure

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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.

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CONTENTS

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).

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9 FIGURES AND TABLES

Figure 1. Study flow-chart.

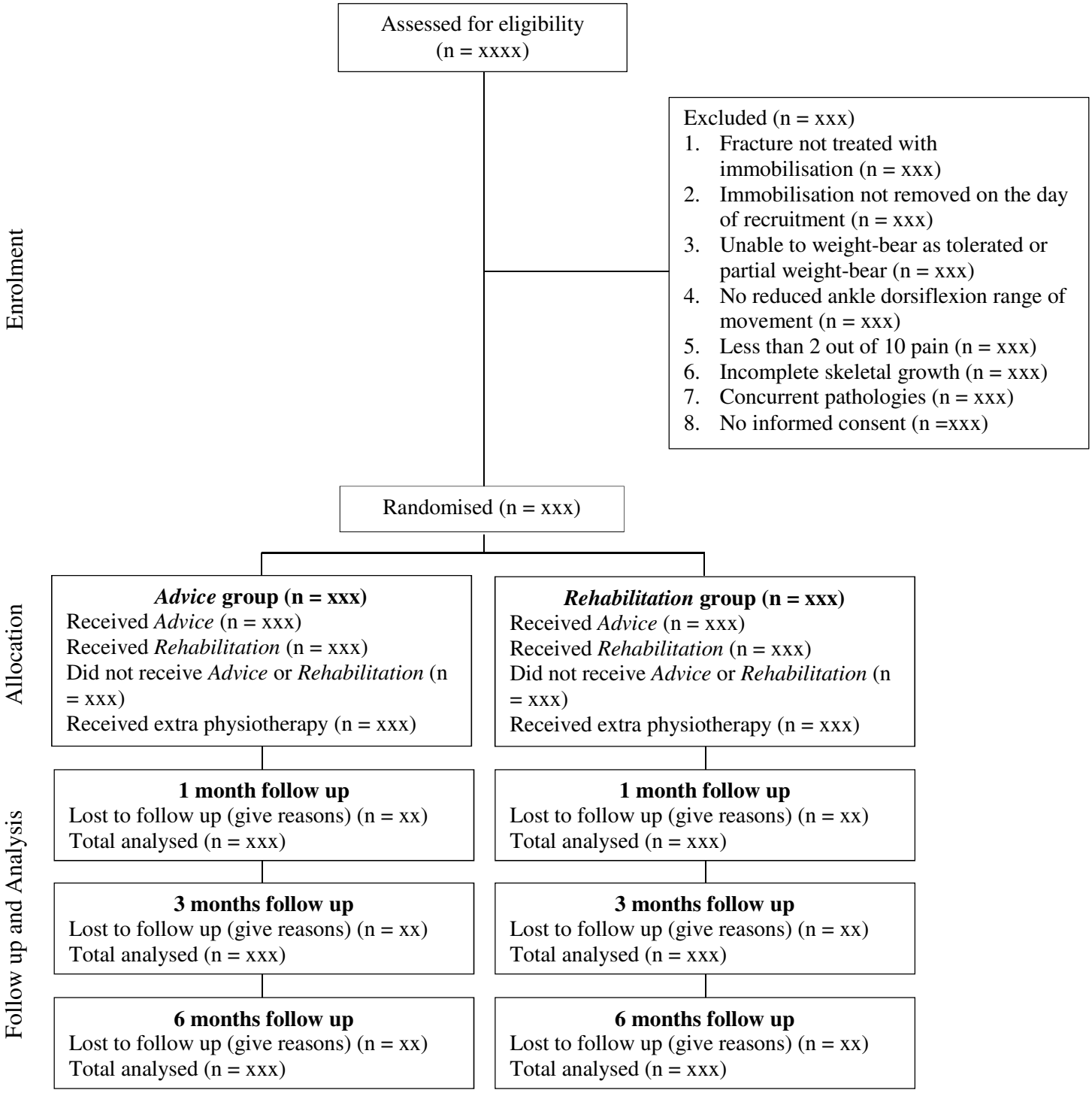

Table 1. Baseline characteristics of the study participants. Continuous variables are presented as means (SD) and categorical as frequency counts (%).

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

Unaided walking speed, m/sec	xx.x (xx.x)	xx.x (xx.x)
Ankle dorsiflexion range of motion, mm**	xx.x (xx.x)	xx.x (xx.x)

* 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.

Variables	*Advice* 1 month (n=xxx)	*Rehab* 1 month (n=xxx)	Difference 1 month	*Advice* 3 months (n=xxx)	*Rehab* 3 months (n=xxx)	Difference 3 months	*Advice* 6 months (n=xxx)	*Rehab* 6 months (n=xxx)	Difference 6 months
Lower Extremity Functional Scale (0-80)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)
Quality adjusted life years (0-1)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)

* $p < 0.05$

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).

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

Health-related quality of life - - social relationships domain (0-9)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)
Health-related quality of life - - physical senses domain (0-9)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)
Health-related quality of life - - psychological well-being domain (0-9)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x - xx.x)

[*] 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 (%).

Variables	*Advice* group (n=xxx)	*Rehabilitation* group (n=xxx)
Percentage of study days on which study exercises were performed	xx.x (xx)	xx.x (xx)
Duration of rehabilitation (days)	NA	xx.x (xx)
Reason for discharge from rehabilitation		
X	NA	n (%)
Y	NA	n (%)
Z	NA	n (%)
Number of physiotherapy sessions attended	NA	xx.x (xx)
Percentage of scheduled physiotherapy sessions attended	NA	xx.x (xx)
Exercises used in rehabilitation program		
1A : 1B : 1C : 1D : 1E	NA	n (%) : n (%) : n (%) : n (%) : n (%)
2A : 2B : 2C : 2D : 2E	NA	n (%) : n (%) : n (%) : n (%) : n (%)
3A : 3B : 3C : 3D : 3E	NA	n (%) : n (%) : n (%) : n (%) : n (%)
Implemented other exercises	NA	n (%)
X	NA	n (%)
Y	NA	n (%)
Z	NA	n (%)
Implemented passive stretches	NA	n (%)
X	NA	n (%)
Y	NA	n (%)
Z	NA	n (%)
Implemented manual therapy	NA	n (%)
X	NA	n (%)
Y	NA	n (%)
Z	NA	n (%)
Implemented other interventions	NA	n (%)
X	NA	n (%)
Y	NA	n (%)
Z	NA	n (%)
Assessor beliefs about group allocation		
1 month knows *Advice* : guesses *Advice* : guesses *Rehabilitation* : knows *Rehabilitation*	n (%) : n (%) : n (%) : n (%)	n (%) : n (%) : n (%) : n (%)
3 month knows *Advice* : guesses *Advice* : guesses *Rehabilitation* : knows *Rehabilitation*	n (%) : n (%) : n (%) : n (%)	n (%) : n (%) : n (%) : n (%)
6 month knows *Advice* : guesses *Advice* : guesses *Rehabilitation* : knows *Rehabilitation*	n (%) : n (%) : n (%) : n (%)	n (%) : n (%) : n (%) : n (%)

NA=not assessed for this group.

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

Variables	*Advice* group (n=xxx)	*Rehabilitation* group (n=xxx)	Between-group difference	Unit cost
Consultations				
Hospital physiotherapist	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	43.80/hour[1]
Private physiotherapist	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	Actual costs as reported by participants
Medical specialist	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	75.50/visit[2]
General practitioner	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	36.30/visit[2]
Alternative health services	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	Actual costs as reported by participants
Hospital				
Emergency department visit	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	347.75/visit[3]
Admission	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	7,630.11/separation[4]
Prescription medication				
% of participants using	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	Various[5]
Other resources				
% of participants using resources not captured above	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)	Actual costs as reported by participants

Sources of valuation:
[1]New South Wales Health Service Health Professionals Award, http://www.health.nsw.gov.au/careers/conditions/Awards/hsu_health_professional.pdf
[2]Australian Government's Medicare Benefits Schedule (MBS), http://www.mbsonline.gov.au/
[3]Reeve R, Haas M (2013) Estimating the cost of emergency department presentations in NSW. Working paper 2014-01. Centre for Health Economics Research and Evaluation (CHERE), University of Technology, Sydney: Ultimo.
[4]New South Wales Costs of Care Standards 2009/10, http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf
[5]Australian Government's Pharmaceutical Benefits Scheme (PBS), http://www.pbs.gov.au/pbs/home

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

Variables	*Advice* group (n=xxx)	*Rehabilitation* group (n=xxx)	Between-group difference
Direct cost to healthcare system[1]	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)
Out-of-pocket cost[2]	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)
Total	xx.x (xx)	xx.x (xx)	xx.x (xx.x - xx.x)

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

[2]Includes 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.