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Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail older people. Study protocol for a randomised controlled trial.

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Key words: frail elderly; randomized controlled trial; therapeutics; exercise.

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ABSTRACT

Introduction: Frailty is a major concern due to its costly and widespread consequences, yet evidence of effective interventions to delay or reduce frailty is lacking. Our previous study found that a multifactorial intervention was feasible and effective in reducing frailty in older people who were already frail. Identifying and treating people in the pre-frail state may be an effective means to preventing or delaying frailty. This study describes a randomised controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on development of frailty in older people who are pre-frail.

Methods and analysis: A single centre, randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis. Two hundred and thirty people aged over 70 who meet the Cardiovascular Health Study frailty criteria for pre-frailty, reside in the community and are without severe cognitive impairment will be recruited. Participants will be randomised to receive a multifactorial intervention or usual care. The intervention group will receive a 12-month interdisciplinary intervention targeting identified characteristics of frailty and problems identified during geriatric assessment. Participants will be followed for a 12-month period. Primary outcome measures will be degree of frailty measured by the number of Cardiovascular Health Study frailty criteria present, and mobility, measured with the Short Physical Performance Battery. Secondary outcomes will include measures of mobility, mood and use of health and community services.

Ethics and dissemination: The study was approved by the Northern Sydney Local Health District Health Research Ethics Committee (1207-213M). The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12613000043730.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First randomised controlled trial to evaluate the effectiveness of an intervention on the development of frailty in older people who are pre-frail.

- Single centre randomised controlled trial with blinded assessors and intention-to-treat analysis.

- Generalisable to community-dwelling pre-frail older people; there is an objective measure of pre-frailty and minimal exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

- Lack of blinding of participants and staff delivering the intervention due to the nature of the intervention.

Data category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry: ACTRN12613000043730
Date of registration in primary registry	14 January 2013
Secondary identifying numbers	Northern Sydney Local Health District Health Research Ethics Committee, Research Protocol Number 1207-213M
Source(s) of monetary or material support	Doris Whiting Special Purpose aand Trust Fund
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Public title	Pre-frailty Intervention Trial. A multifactorial interdisciplinary treatment program for older people who are pre-frail
Scientific title	Pre-frailty Intervention Trial (Pre-FIT). The effects of an interdisciplinary multifactorial intervention versus usual care on pre-frailty and mobility function in pre-frail older people
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Pre-frailty
Intervention(s)	Intervention group: Participants in the intervention group will receive a multifactorial, interdisciplinary treatment program intended to target the frailty criteria that are present for a 12-month period following randomisation. The interventions will be individually tailored to each participant based on their frailty characteristics as assessed at baseline, and additional problems as identified during a detailed assessment by experienced physiotherapist providing the intervention program. Geriatric evaluation and management principles will underpin both the assessment and intervention. Case management and regular case conferences will facilitate coordination of intervention delivery. Reassessment will be ongoing throughout the intervention phase. Control: Participants in the control group will receive the usual healthcare available to older residents in the Hornsby Ku-ring-gai area from their General Practitioner and community services.
Key inclusion and exclusion	Ages eligible for study: ≥70 years

criteria	Sexes eligible for study: both Inclusion criteria: Meet one or two of the Cardiovascular Health Study frailty criteria, and thus are considered pre-frail. Have mild or no cognitive impairment (defined as a Mini Mental State Examination score of more than 23) Exclusion criteria: Living in a residential aged care facility Have an estimated life expectancy of less than 12 months (estimated by a score of ≤3 on a modified version of the Implicit Illness Severity Scale) Currently receiving a treatment program from a rehabilitation facility
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blind (outcome assessor) Primary purpose: prevention
Date of first enrolment	14 January 2013
Target sample size	230
Recruitment status	Recruitment completed 07 October 2014
Primary outcome(s)	Pre frailty (which is the presence of one or two of the five Cardiovascular Health Study frailty criteria) Short Physical Performance Battery
Key secondary outcomes	Quality of Life as assessed by EQ-5D and VAS, Barthel Index, Activity Measure for Post-Acute Care, Gait speed (4 meter walk test), falls, hospitalisation, move to residential aged care facility.

Date: 2 November 2015, Version 1.

INTRODUCTION

Intervention to prevent or delay frailty has important benefits for older people, health services and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by reduced strength, endurance and physiologic function, resulting in increased vulnerability to functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between non-frail and frail. Identifying and treating people in the pre-frail state may be an effective way to prevent or delay frailty.

Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3] which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria, and frail if they meet three or more criteria. The frailty phenotype is predictive of falls, disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have significantly higher risk of developing these adverse outcomes than non-frail people, and frail individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic review found the prevalence of pre-frailty (as defined by the frailty phenotype) in community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is rising globally, the costs associated with frailty will increase in the future. Preventing or delaying frailty has the potential to reduce the burden on individuals and society.

Research into interventions to prevent or reduce frailty is in its infancy. While studies have found that outcomes for frail older people can be improved using multi-factorial interventions such as comprehensive geriatric assessment, and single interventions including exercise

programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome (measured using the frailty phenotype), and found the intervention significantly reduced frailty in frail community-dwelling older people.[7]

Implementing interventions to pre-frail older people may prevent the development of frailty. Older people transition between frailty states,[8] and pre-frail individuals have more than twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to frail is often endues from an acute medical event or a psychological stress exceeding the person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the impact of potential stressors may therefore reduce the risk of becoming frail. Evidence suggests pre-frail older people may respond better to intervention than people who have already moved to a frail state,[10,11] and because pre-frail people have significantly less disability than frail people [3] there is potential for more intensive interventions.

Few trials have identified and targeted pre-frail participants. Previous trials have included samples that are probably pre-frail, for example people at risk of falling,[12] however studies need to have pre-frailty as an inclusion criteria for results to be generalisable to this population. Recent randomised trials [10,13,14] and an observational study [15] have investigated the effects of exercise in people defined as pre-frail using the frailty phenotype; exercise appears to improve function in pre-frail people, however larger studies are needed. To our knowledge, no intervention has been developed to specifically prevent the transition to frailty in pre-frail older people.

We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial that aims to determine whether delivering a multifactorial, interdisciplinary intervention to older people who are pre-frail prevents progression to frailty and improves mobility. We will implement a modification of the intervention previously found to reduce frailty and improve mobility in frail older people [16] to determine whether pre-frail participants receive similar benefits with respect to frailty levels and mobility. To our knowledge this will be the first study to examine the effects of an intervention specifically targeting degree of frailty among older people who are pre-frail. The primary research question is: Does the multifactorial interdisciplinary intervention prevent the progression to frailty (assessed with a frailty phenotype score) and improve mobility among pre-frail older people, when compared with usual care?

METHODS AND DESIGN

Design

A single-centre, randomised controlled trial will be conducted among 230 participants who are pre-frail. Figure 1 gives an overview of the study design. The Northern Sydney Local Health District Health Research Ethics Committee approved this study (Research Protocol Number 1207-213M) and all participants will give written informed consent prior to randomisation (Appendix 1). The study is registered with the Australia New Zealand Clinical Trials Register ACTRN12613000043730.

Participants

Potential participants will be identified by clinicians working in hospital and community sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-ring-gai Health Service, in Sydney, Australia.

Participants who fulfill the following inclusion criteria will be invited to participate:

1. Male or female, aged 70 years or older
2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)
3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score > 23);

People will be ineligible to participate in the trial if they:

1. Live in a residential aged care facility
2. Have an estimated life expectancy of less than 12 months (estimated by a score of ≤3 on a modified version of the Implicit Illness Severity Scale [18])
3. Currently receive a treatment program from a rehabilitation facility

Table 1.

Characteristic	Criteria
Weight loss/ Shrinking	Self-report of ≥ 4.5 kg lost unintentionally in previous 12 months or loss of ≥5% of weight in prior year by direct measurement of weight
Weakness	Lowest 20% in grip strength, measured using a dynamometer (Saehen Dynamometer, model SH5001). Best of three attempts used. Males scoring 30kg or less, female scoring 18kg or less meet the criteria
Exhaustion	Answering "a moderate amount" or "most of the time" to either of the 2 questions from the Centre for Epidemiological Studies-Depression Scale (CES-D) indicated exhaustion: "How often did you feel that everything you did was an effort in the last week?" or "How often did you feel that you could not get going in the last week?".
Slowness	Time to walk four metres, with or without a walking aid, equals six seconds or more.

Low activity	In the past three months, weight bearing physical activity was not performed, more than four hours per day were spent sitting, and went for a short walk once per month or less.

Randomisation

After consent and completion of the baseline assessment, participants will be entered into the study and randomised to intervention or control groups. Permuted block randomisation will be used,[19] with a random number sequence generated by SPSS v19 and variable block sizes randomly arranged within larger blocks. Project personnel not otherwise involved in recruitment or data collection will manage random group allocation. The treatment allocation tables will be stored away from the research office.

Allocation concealment

The Research Consultant will screen for study eligibility, seek informed consent and conduct the baseline assessment. After baseline assessment is completed, the Research Consultant will telephone the central study office, and the participant will be assigned a participant number and allocated to the control or intervention group. Staff performing the outcome assessment and data analysis will be blinded to group allocation, however due to the nature of the trial it is not possible to blind the participants and staff administering interventions.

Intervention

Participants assigned to the control group will receive the usual care available to older residents of Hornsby Ku-ring-gai area from their general practitioner and community services. At the study site, usual care for non-institutionalised pre-frail older people involves

medical management of health conditions, allied health input, assessment of care needs and provision of care.

Participants in the intervention group will receive an interdisciplinary, multifactorial intervention for one year. The intervention will be individually tailored to each participant based on the following: a) the CHS frailty characteristics present at baseline assessment; b) additional problems identified during a detailed assessment by the physiotherapist providing the intervention program, plus other relevant members of the interdisciplinary team; c) ongoing reassessment by the interdisciplinary team throughout the intervention period. The assessment and intervention will be underpinned by the principles of geriatric evaluation and management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician, a rehabilitation physician, a dietician and a nurse will deliver the intervention. All intervention staff will have experience in delivering interventions to older people. Case management and regular case conferences will assist coordination of the interdisciplinary delivery of the intervention. The treating physiotherapist will have the case coordinator role, liaising with the participant, family, health professionals and service providers, plus coordinating services as indicated.

The intervention will be delivered primarily in participants' homes, with additional community exercise programs and outpatient appointments (for example, podiatrist, memory clinic, continence clinic) offered when indicated.

The interventions targeting the CHS frailty characteristics are described below.

Weight loss

A dietician will evaluate nutritional intake if the participant is not already effectively addressing their recent weight loss. If the participant's body mass index is <18.5 or mid upper arm circumference is < the 10th percentile (using Australian gender and age specific norms), nutritional supplementation will be offered using commercially available, high protein, high energy, supplements. Home delivered meals will be recommended if appropriate clinical criteria apply.

Exhaustion

Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale score is high. Where the participant is socially isolated, opportunities to encourage greater social engagement will be identified, e.g. day activity groups, physical activity programs in the community, and telephone contact with volunteers.

Grip weakness, slow four metre walk time, or low physical activity level

A physiotherapist experienced in aged care will visit the participant's home ten times in the 12 months study period. There will be five sessions in the first three months after randomisation, and five sessions over the following nine months. Visits will be 60 to 120 minutes duration. The physiotherapist will prescribe a home exercise program to be performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree of difficulty and number of repetitions prescribed will be based upon assessment of the individual participant's abilities. Lower limb balance and strengthening exercises will utilise the Weight Bearing Exercise for Better Balance (WEBB) program, available at www.webb.org.au.[22] The program targets strength and control of the lower limb extensor muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a

wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as appropriate. Balance will be targeted with exercises performed in standing with a progressively narrowed base (feet together, tandem stance, single leg stance), stepping, walking and reaching. Upper limb support will be minimised in order to adequately challenge balance, but to ensure safety the environment will be set up with stable supports (e.g. bench or table) close by that can be held as necessary. In addition, if upper limb weakness is creating functional problems, then the physiotherapist may prescribe upper limb exercises incorporating theraband or free weights for resistance. The physiotherapist will regularly review and modify the optimal intensity and type of exercises for each participant to ensure the intervention remains appropriate and challenging over the study period. We will encourage family members or carers to assist with the exercise program when this is indicated.

Appropriate safe mobility programs will be prescribed if participants have low activity levels, reduced endurance or specific functional goals. Feedback will be provided via monitoring of distance/time or via a pedometer or *FitBit (*internet-linked pedometer). Participants will be encouraged and supported in increasing their physical activity using exercise equipment that they have at home, as well as community physical activity programs (such as Tai Chi or strength and balance classes), community exercise facilities (such as gymnasiums and swimming pools) and a return to past leisure activities such as golf and bowls.

In addition to the interventions targeting the CHS frailty characteristics, individually-tailored intervention will address additional problems identified during assessment. Intervention may include, but will not be limited to, the following examples.

- General health status will be assessed and intervention tailored to each individual's problems. Where indicated, chronic disease management programs will be implemented or reinforced in conjunction with existing health services. We will use the principles of comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and conditions such as incontinence, osteoporosis and impaired cognition.
- The rehabilitation physician or geriatrician will review medications used and will discuss any questionable medication use with the participant's general practitioner. Poor compliance with medications will be addressed by initiation or reinforcement of strategies such as education about medications, medication packaging in blister packs and reminder cards.
- Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia, and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and Parkinson's Disease exercise classes.
- The team will refer to agencies that provide assessments and provision of care and services. Examples are the Aged Care Assessment Team for assessment for packages of care, community nursing and service providers.
- If transport is required, we will arrange referral to community transport services, taxi subsidy schemes and mobility parking schemes as appropriate.
- Reduced social interaction will be targeted by facilitating attendance at community-based groups, day centres, clubs and exercise groups, as well as by arranging telephone contact with a volunteer.
- We will advise on meal delivery services and frozen meals if this assistance is needed.
- Mobility aids and other equipment will be recommended, obtained and set up where indicated. This may involve referral to an occupational therapist for environmental modifications.
- Advice on appropriate footwear will be provided if shoes are suboptimal.

- Ergonomic alterations will be made to optimise home office safety.
- If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program) available in the study area, in addition to the WEBB exercise program. Safety concerns will also be addressed with information about falls prevention, personal alarms and hip protectors.
- If the participant cares for another person or the participant has a carer who needs help, the carer's needs will be assessed and contact with Carers Australia will be suggested.

The physiotherapist and participant will collaborate to set measurable goals within three months of recruitment. The goals will be based upon the CHS frailty characteristics present (such as goals relating to diet, functional consequences of weakness or amount of physical activity), or problems identified during geriatric assessment (such as establishing formal links with a diabetes educator, understanding medications or obtaining a care package). The goals will be documented, reviewed each session by the physiotherapist and participant, and new goals will be set when new issues are targeted.

The physiotherapist will promote adherence to the intervention using strategies including goal setting, a flexible time-frame for intervention delivery, recording of exercise completion, and involvement of family and carers. In addition, programs will be tailored to suit individual requirements and safety concerns, and interventions will be designed to be varied, sustainable and enjoyable.

Data collection

Participants will undergo three home-based assessments. The baseline measures will be assessed prior to randomisation and further assessments will be conducted four and 12

months after randomisation. Additional health service utilisation data will be collected via a telephone call at eight months. Blinded assessors (experienced health professionals, trained in conducting the outcome measures) will conduct follow-up assessments. To ensure blinding, participants will be instructed not to disclose group allocation to the assessors. The assessors' perception of group allocation will be assessed, to evaluate the success of assessor blinding. The data collection forms are available from the authors. Personal information and data will be collated on paper forms and entered in a Microsoft Access using range checks for data values. Paper files will be stored in a locked filing cabinet and electronic information will be stored in a password protected computer. The research documents will be kept for at least 5 years after study completion. The final trial dataset will be available to trial authors who are undertaking data analysis for presentations or publications.

Outcome measures

Demographic and health information will be collected at baseline. Cognitive function will be assessed with the Mini Mental State Examination.[23]

- *Primary outcomes*

The primary outcomes measured are frailty and mobility, measured at four and 12 months. Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty phenotype evaluates five components of the frailty syndrome and allocates one point for each criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using the lower extremity continuous summary performance score (CSPS),[24] with data collected using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem positions, time taken to walk four metres, and time to rise from a chair and return to the

seated position five times.

- *Secondary outcomes*

1. Psychological status will be assessed using the five-item version of the Geriatric Depression Scale.[26]
2. Activities of daily living will be measured using the Barthel Index [27] (100 point version). The mobility component of the Activity Measure for Post Acute Care [28] will measure self reported activity level using Item Response Theory and computer-adaptive testing.
3. Gait speed will be measured using the four-metre walk test.
4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility weights to allow calculation of Quality adjusted life years (QALYs) for use in the economic evaluation.[29]
5. Falls, hospitalisations and admissions to residential aged care facilities will be collected via telephone at four, eight and 12 months and will also be used in the economic analyses.
6. Health and community service use will be recorded at four, eight and 12 months and will be used in economic analyses.

- *Additional measures*

Adherence measurements will record the acceptance of health and other services by the study participant. The treating physiotherapist will estimate a global level of adherence (in five categories: 0%, <25%, 25-49%, 50-74% and ≥75%) during the 12-month intervention. The treating physiotherapist will evaluate goal attainment in the intervention group using a four-point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal exceeded.

Adverse events will be defined as medical events or injuries arising as a consequence of the trial and resulting in medical attention or restricted activities of daily living for more than two days.[30] Deaths will be documented. The intervention staff will report adverse events and deaths to the Chief Investigator within two days and they will be discussed at the next case conference.

Sample size calculation

An *a priori* power analysis determined 230 participants will need to be recruited, to provide 80% power to detect a clinically and statistically significant 15% between group difference in lower extremity continuous summary performance score (SD = 0.7).[25] This sample size will also provide sufficient power to detect a clinically meaningful 20% between-group difference in transition to frailty. For these calculations, we assumed an α of 0.05, non-compliance of 15% and a dropout rate of 15%.

Statistical analysis

Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable. The other study outcomes will be treated as continuous variables. The effect of group allocation on continuously scored outcome measures at the four month and twelve month follow-ups will be analysed using linear regression models with baseline scores entered into the linear regression models as covariates. To aid interpretation of the change in frailty, frailty will also be reported as a continuous variable. Statistical significance will be set at $P<0.05$ and we will report the differences in percentage or mean (95% confidence interval) between the two groups at the 4-month and 12-month follow-ups.

We will test whether the response to the intervention is modified by the number of frailty

criteria present at baseline, by including an interaction term of study groups with number of frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to 74% and ≥75%) on the outcomes in the intervention group at 12-month follow-up. We will examine baseline variables and if there are important between group differences we will adjust for them in the models. The primary analyses will be conducted in accordance with the intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in the statistical analysis. The data monitoring committee, consisting of the Chief Investigator and experienced researchers independent from the trial and funding, will analyse the between-group difference in deaths every six months.

Economic evaluation

The economic evaluation will be carried out and reported in accordance with health economics reporting standards.[33] The economic evaluation will take the perspective of Australian health and aged care service providers over a 12-month time period. Benefits will be measured in terms of number of transitions to frailty prevented, mobility improvement and QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness analyses will include the cost of delivering the intervention and the cost of health and community service utilisation. Bootstrap sampling will be used to examine the joint probability distribution of costs and outcomes, with the creation of incremental cost-effectiveness planes and cost-effectiveness acceptability curves for each outcome.

Timeframe

Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in October 2015.

DISCUSSION

This trial will provide important information to guide intervention to improve outcomes for older people who are pre-frail. Specifically, it will determine whether a multifactorial interdisciplinary intervention reduces transition to frailty and deterioration in mobility among pre-frail older men and women who live in the community. Frailty and the associated negative effects such as disability, institutionalisation and hospitalisation are costly to individuals, their families, the health system and society. Despite this cost, to our knowledge there has been no research to date examining the effectiveness of intervention designed to reduce the transition to frailty among pre-frail older people.

The proposed multifactorial intervention will target the needs of each participant based upon the characteristics of frailty present and comprehensive geriatric assessment. The exercise component was designed using evidence from systematic reviews and randomised trials that have demonstrated improved strength, balance and mobility in older people. We will implement strategies to maximise adherence to the intervention, in line with research suggesting good patient adherence increases the effectiveness of health interventions.[7,34] The intervention is based on the program that was feasibly delivered to frail older people in the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to balance, strength and physical activity. Tailoring the exercises to the individual and ongoing reassessment by the treating physiotherapist will ensure safety.

Additional strengths of the study are the generalisability to pre-frail older people and aged care health service settings, and the robust, but pragmatic, clinical trial design. This study uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in

the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

This study has some limitations. First, participants cannot be blinded to group allocation, which is a potential source of bias due to possible differential reporting of the weight loss, activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria, and the co-primary outcome measure (CSPS) are performance-based, which should reduce this bias. Second, as there is no frequency-matched social intervention for the control group, we will not be able to exclude the impact of social aspects of the program on any difference between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the CHS phenotype is the most widely accepted instrument, other validated tools [36] and attention to cognition could be considered in the clinical setting.

If this intervention is shown to be effective, there are major potential benefits to the older population in terms of preventing transition to frailty and improving mobility. Avoiding frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation and institutionalisation, and the associated financial costs. Improved mobility may also result in improved function and better quality of life for older people, their families and carers. If cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of health services. The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

List of abbreviations used

CHS: Cardiovascular Health Study

Pre-FIT: Pre-Frailty Intervention Trial

WEBB: Weight Bearing Exercise for Better Balance

SPPB: Short Physical Performance Battery

SD: standard deviation

QALYs: Quality adjusted life years

CSPS: lower extremity continuous summary performance score

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Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

NF drafted the manuscript. All authors are actively involved in the study. All authors read and approved the final manuscript.

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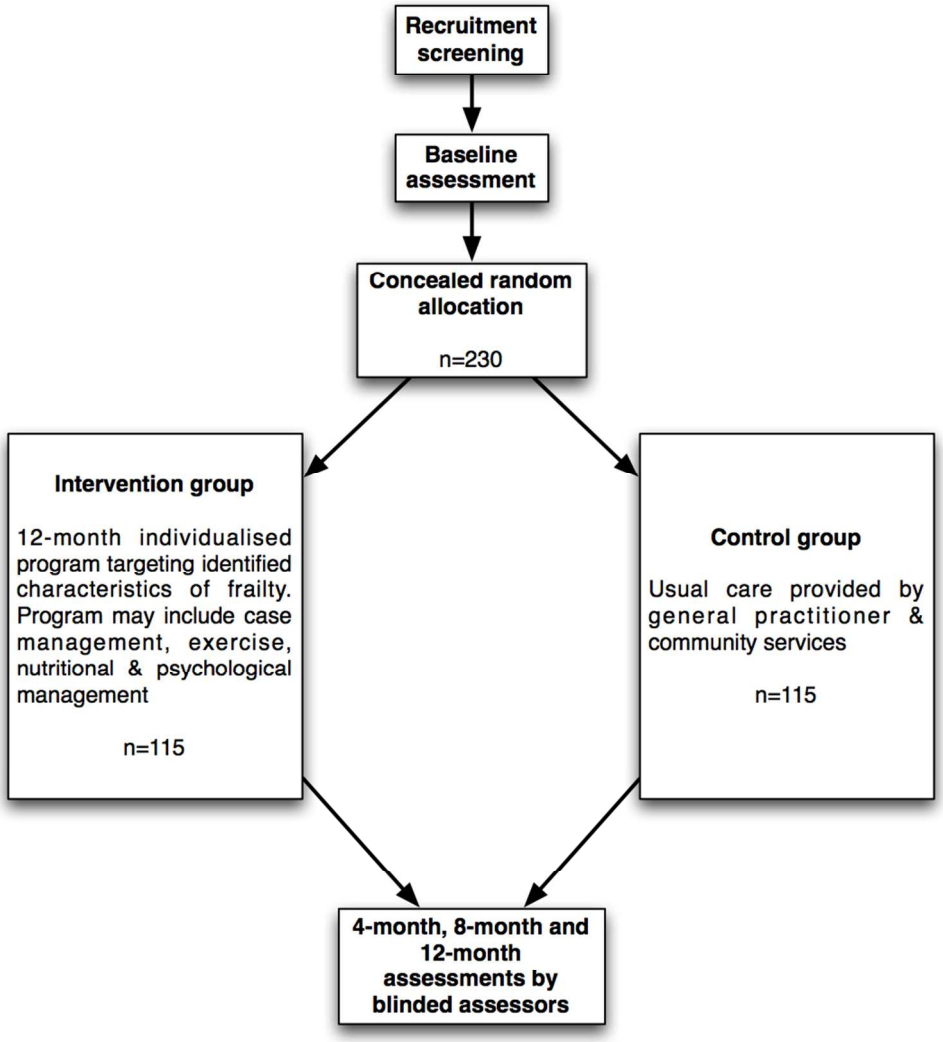
Figures

Figure 1. Overview of the flow of participants through the Pre-frailty Intervention Trial

Appendix 1. Informed consent form



Overview of the flow of participants through the Pre-frailty Intervention Trial
187x205mm (150 x 150 DPI)

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

Invitation
You are invited to participate in a research study investigating the effectiveness of a specialised treatment program for older people who are pre-frail.

The study is being conducted by Hornsby Ku-ring-gai Hospital and the Rehabilitation Studies Unit (University of Sydney).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the purpose of this study?
The purpose is to investigate whether or not a program involving contact with one or several health professionals over a period of approximately 12 months is effective in improving the overall health of people who are pre-frail. The study definition of pre-frail requires that participants have one or two criteria that have been linked to frailty in a previous study (The Cardiovascular Health Study). These criteria are: 1. Unexplained weight loss in the past year. 2. Diminished grip strength. 3. Self reported exhaustion. 4. Sow gait speed and 5. low energy expenditure.

2. Why have I been invited to participate in this study?
You are eligible to participate in this study because you are aged over 70 years, and may meet our definition of being pre-frail.

3. What if I don't want to take part in this study or if I want to withdraw later?
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect any treatment you receive now or in the future. Whatever your decision, it will not affect any future relationship with Hornsby Hospital or The University of Sydney.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

4. What are the alternatives to participating in this study?

If you decide not to participate in this study, you will still receive the standard treatment and care as would otherwise normally have been available to you in this area, generally accessible following consultation with your general practitioner.

5. What does this study involve?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form attached to this information sheet.

This study will be conducted over a period of 12 months.

This project is a randomised trial. If you agree to participate you will be put into one of two groups. One group will receive the multifactorial intervention while the other group will receive the 'usual care' that would otherwise have been available to them. Both groups will receive visits from our research team over a12 month period. The results will be compared to see whether one treatment is more effective than the other. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the researcher nor the study participant can decide which group the participant will be allocated to. You will be told which group you are in.

All participants will be asked to complete three assessments with a study research nurse. One assessment is conducted at the commencement of the study, one after four months and the final assessment at the end of your involvement with the study (at 12 months). These assessments involve some minor strength and balance testing and some questions about your health, well being and service usage.

In addition, the researchers may require access to your hospital medical records in order
to obtain information relevant to the study.

6. How is this study being paid for?

The study is being sponsored by a trust fund connected to the Rehabilitation and Aged Care Service at Hornsby Ku-ring-gai Hospital. No money (besides normal salary) is paid directly to any individual researchers.

7. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, it is possible you could develop a medical complication from participating in this study. Based on our experience there is a small risk that a

musculoskeletal symptom may develop as a result of the physical therapy intervention. This could be in the form of a muscular strain, or minor stress to ligaments or joint. In this unlikely event, the exercise program will be modified. There is also a slight risk of falling while exercising and this possibility will also be monitored.

8. What happens if I suffer injury or complications as a result of the study?
If you suffer any injuries or complications as a result of this study, you should contact the researcher visiting you as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the project intervention or by the negligence of any of the research staff who visit you. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

9. Will I benefit from the study?
This study aims to further develop medical knowledge and may improve future treatment of frailty; it may or may not be of direct benefit you.

10. Will taking part in this study cost me anything, and will I be paid?
Participation in this study will not cost you anything; neither will you be paid for your participation.

11. How will my confidentiality be protected?
Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or as required by law. Only the study researchers will have access to your details and results and all information will be held securely at Hornsby Ku-ring-gai Hospital.

12. What happens with the results?
If you give us your permission by signing the consent document, we plan to publish the results of the study in peer reviewed journals at the conclusion of the trial. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. What happens to my treatment when the study is finished?
If you are allocated to the group receiving the intervention, these visits will cease at the end of the study period. Usual community care, assessable through your general practitioner will resume at this point.

14. What should I do if I want to discuss this study further before I decide?
When you have read this information, the research nurse will discuss it with you and address any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her or any member of the project team.

15. Who should I contact if I have concerns about the conduct of this study?
This study has been approved by the Northern Sydney Coast Human Research ethics Committee of Northern Sydney and Central Coast Local Health Districts (NSLHD & CCLHD). Any person with concerns or complaints about the conduct of this study should contact Professor Ian Cameron at the Rehabilitation Studies Unit on (02) 9808-9236 or alternatively the Research Office on (02) 9926 8106 and quote " The Pre-frailty Intervention Trial" (Pre-FIT).

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

1. I,.....

   of.....

   .....

   agree to participate as a subject in the study described in the attached participant information statement : **Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail.**

2. I acknowledge that I have read the participant information statement, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

4. I understand that I can withdraw from the study at any time without prejudice to my relationship to the University of Sydney or Hornsby Ku-ring-gai Hospital Health Service.

5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

6. I understand that if I have any questions relating to my participation in this research, I may contact Professor Ian Cameron on telephone (02) 9808-9236 who will be happy to answer them.

7. I give my consent for my hospital records to be accessed for the purposes of this research if necessary.

8. I acknowledge receipt of a copy of this Consent Form and the Participant Information Statement.

I understand that should I have a complaint in regards to the conduct of this trial it may be directed to either Professor Ian Cameron on telephone (02) 9808-9236 or the Northern Sydney Coast Human Research Ethics Committee on (02) 9926 8106.

Signature of subject	**Please PRINT name**	**Date**

Signature of Researcher	**Please PRINT name**	**Date**

Health
Northern Sydney
Local Health District

NSW GOVERNMENT

Hornby Ku-ring-gai Health Service

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the University of Sydney or Hornsby Ku-ring-gai Hospital

Signature……..…….. Date…../…../…..

Please PRINT Name:……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	5,6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	11,12
Objectives	7	Specific objectives or hypotheses	9

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16,18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17,18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16,17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19,20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19,20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Randomisation

The following information about block sizes was omitted from the protocol to ensure the information is unavailable to personnel enrolling participants and assigning interventions.

Permuted block randomisation will be used, with a random number sequence generated by SPSS v19 and variable block sizes of four and six randomly arranged within blocks of 10.

BMJ Open

Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail older people. Study protocol for a randomised controlled trial.

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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	GERIATRIC MEDICINE, frail elderly, randomised trial

Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail older people. Study protocol for a randomised controlled trial.

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Key words: frail elderly; randomized controlled trial; therapeutics; exercise.

Word count: 3913

ABSTRACT

Introduction: Frailty is a major concern due to its costly and widespread consequences, yet evidence of effective interventions to delay or reduce frailty is lacking. Our previous study found that a multifactorial intervention was feasible and effective in reducing frailty in older people who were already frail. Identifying and treating people in the pre-frail state may be an effective means to preventing or delaying frailty. This study describes a randomised controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on development of frailty in older people who are pre-frail.

Methods and analysis: A single centre, randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis. Two hundred and thirty people aged over 70 who meet the Cardiovascular Health Study frailty criteria for pre-frailty, reside in the community and are without severe cognitive impairment will be recruited. Participants will be randomised to receive a multifactorial intervention or usual care. The intervention group will receive a 12-month interdisciplinary intervention targeting identified characteristics of frailty and problems identified during geriatric assessment. Participants will be followed for a 12-month period. Primary outcome measures will be degree of frailty measured by the number of Cardiovascular Health Study frailty criteria present, and mobility, measured with the Short Physical Performance Battery. Secondary outcomes will include measures of mobility, mood and use of health and community services.

Ethics and dissemination: The study was approved by the Northern Sydney Local Health District Health Research Ethics Committee (1207-213M). The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12613000043730.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First randomised controlled trail to evaluate the effectiveness of an intervention on the development of frailty in older people who are pre-frail.

- Randomised controlled trial with blinded assessors and intention-to-treat analysis.

- Generalisable to community-dwelling pre-frail older people; there is an objective measure of pre-frailty and minimal exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

- Lack of blinding of participants and staff delivering the intervention due to the nature of the intervention.

INTRODUCTION

Intervention to prevent or delay frailty has important benefits for older people, health services and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by reduced strength, endurance and physiologic function, resulting in increased vulnerability to functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between non-frail and frail. Identifying and treating people in the pre-frail state may be an effective way to prevent or delay frailty.

Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3] which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria, and frail if they meet three or more criteria. The frailty phenotype is predictive of falls, disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have significantly higher risk of developing these adverse outcomes than non-frail people, and frail individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic review found the prevalence of pre-frailty (as defined by the frailty phenotype) in community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is rising globally, the costs associated with frailty will increase in the future. Preventing or delaying frailty has the potential to reduce the burden on individuals and society.

Research into interventions to prevent or reduce frailty is in its infancy. While studies have found that outcomes for frail older people can be improved using multi-factorial interventions such as comprehensive geriatric assessment, and single interventions including exercise

programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome (measured using the frailty phenotype), and found the intervention significantly reduced frailty in frail community-dwelling older people.[7]

Implementing interventions to pre-frail older people may prevent the development of frailty. Older people transition between frailty states,[8] and pre-frail individuals have more than twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to frail is often endues from an acute medical event or a psychological stress exceeding the person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the impact of potential stressors may therefore reduce the risk of becoming frail. Evidence suggests pre-frail older people may respond better to intervention than people who have already moved to a frail state,[10,11] and because pre-frail people have significantly less disability than frail people [3] there is potential for more intensive interventions.

Few trials have identified and targeted pre-frail participants. Previous trials have included samples that are probably pre-frail, for example people at risk of falling,[12] however studies need to have pre-frailty as an inclusion criteria for results to be generalisable to this population. Recent randomised trials [10,13,14] and an observational study [15] have investigated the effects of exercise in people defined as pre-frail using the frailty phenotype; exercise appears to improve function in pre-frail people, however larger studies are needed. To our knowledge, no intervention has been developed to specifically prevent the transition to frailty in pre-frail older people.

We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial that aims to determine whether delivering a multifactorial, interdisciplinary intervention to older people who are pre-frail prevents progression to frailty and improves mobility. We will implement a modification of the intervention previously found to reduce frailty and improve mobility in frail older people [16] to determine whether pre-frail participants receive similar benefits with respect to frailty levels and mobility. To our knowledge this will be the first study to examine the effects of an intervention specifically targeting degree of frailty among older people who are pre-frail. The primary research question is: Does the multifactorial interdisciplinary intervention prevent the progression to frailty (assessed with a frailty phenotype score) and improve mobility among pre-frail older people, when compared with usual care?

METHODS AND DESIGN

Design

A randomised controlled trial will be conducted among 230 participants who are pre-frail. Figure 1 gives an overview of the study design. The Northern Sydney Local Health District Health Research Ethics Committee approved this study (Research Protocol Number 1207-213M) and all participants will give written informed consent prior to randomisation (Appendix 1). The study is registered with the Australia New Zealand Clinical Trials Register ACTRN12613000043730.

Participants

Potential participants will be identified by clinicians working in hospital and community sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-ring-gai Health Service, in Sydney, Australia.

Participants who fulfill the following inclusion criteria will be invited to participate:

1. Male or female, aged 70 years or older
2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)
3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score > 23);

People will be ineligible to participate in the trial if they:

1. Live in a residential aged care facility
2. Have an estimated life expectancy of less than 12 months (estimated by a score of ≤3 on a modified version of the Implicit Illness Severity Scale [18])
3. Currently receive a treatment program from a rehabilitation facility

Table 1.

Characteristic	Criteria
Weight loss/ Shrinking	Self-report of ≥ 4.5 kg lost unintentionally in previous 12 months or loss of ≥5% of weight in prior year by direct measurement of weight
Weakness	Lowest 20% in grip strength, measured using a dynamometer (Saehen Dynamometer, model SH5001). Best of three attempts used. Males scoring 30kg or less, female scoring 18kg or less meet the criteria
Exhaustion	Answering "a moderate amount" or "most of the time" to either of the 2 questions from the Centre for Epidemiological Studies-Depression Scale (CES-D) indicated exhaustion: "How often did you feel that everything you did was an effort in the last week?" or "How often did you feel that you could not get going in the last week?".
Slowness	Time to walk four metres, with or without a walking aid, equals six seconds or more.

Low activity	In the past three months, weight bearing physical activity was not performed, more than four hours per day were spent sitting, and went for a short walk once per month or less.

Randomisation

After consent and completion of the baseline assessment, participants will be entered into the study and randomised to intervention or control groups. Permuted block randomisation will be used,[19] with a random number sequence generated by SPSS v19 and variable block sizes of four and six randomly arranged within blocks of 10. Project personnel not otherwise involved in recruitment or data collection will manage random group allocation. The treatment allocation tables will be stored away from the research office.

Allocation concealment

The research consultant will screen for study eligibility, seek informed consent and conduct the baseline assessment. After baseline assessment is completed, the Research Consultant will telephone the central study office, and the participant will be assigned a participant number and allocated to the control or intervention group. Staff performing the outcome assessment and data analysis will be blinded to group allocation, however due to the nature of the trial it is not possible to blind the participants and staff administering interventions.

Intervention

Participants assigned to the control group will receive the usual care available to older residents of Hornsby Ku-ring-gai area from their general practitioner and community services. At the study site, usual care for non-institutionalised pre-frail older people involves

medical management of health conditions, allied health input, assessment of care needs and provision of care.

Participants in the intervention group will receive an interdisciplinary, multifactorial intervention for one year. The intervention will be individually tailored to each participant based on the following: a) the CHS frailty characteristics present at baseline assessment; b) additional problems identified during a detailed assessment by the physiotherapist providing the intervention program, plus other relevant members of the interdisciplinary team; c) ongoing reassessment by the interdisciplinary team throughout the intervention period. The assessment and intervention will be underpinned by the principles of geriatric evaluation and management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician, a rehabilitation physician, a dietician and a nurse will deliver the intervention. All intervention staff will have experience in delivering interventions to older people. Case management and regular case conferences will assist coordination of the interdisciplinary delivery of the intervention. The treating physiotherapist will have the case coordinator role, liaising with the participant, family, health professionals and service providers, plus coordinating services as indicated.

The intervention will be delivered primarily in participants' homes, with additional community exercise programs and outpatient appointments (for example, podiatrist, memory clinic, continence clinic) offered when indicated.

The interventions targeting the CHS frailty characteristics are described below.

Weight loss

A dietician will evaluate nutritional intake if the participant is not already effectively addressing their recent weight loss. If the participant's body mass index is <18.5 or mid upper arm circumference is < the 10th percentile (using Australian gender and age specific norms), nutritional supplementation will be offered using commercially available, high protein, high energy, supplements. Home delivered meals will be recommended if appropriate clinical criteria apply.

Exhaustion

Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale score is high. Where the participant is socially isolated, opportunities to encourage greater social engagement will be identified, e.g. day activity groups, physical activity programs in the community, and telephone contact with volunteers.

Grip weakness, slow four metre walk time, or low physical activity level

A physiotherapist experienced in aged care will visit the participant's home ten times in the 12 months study period. There will be five sessions in the first three months after randomisation, and five sessions over the following nine months. Visits will be 60 to 120 minutes duration. The physiotherapist will prescribe a home exercise program to be performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree of difficulty and number of repetitions prescribed will be based upon assessment of the individual participant's abilities. Lower limb balance and strengthening exercises will utilise the Weight Bearing Exercise for Better Balance (WEBB) program, available at www.webb.org.au.[22] The program targets strength and control of the lower limb extensor muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a

wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as appropriate. Balance will be targeted with exercises performed in standing with a progressively narrowed base (feet together, tandem stance, single leg stance), stepping, walking and reaching. Upper limb support will be minimised in order to adequately challenge balance, but to ensure safety the environment will be set up with stable supports (e.g. bench or table) close by that can be held as necessary. In addition, if upper limb weakness is creating functional problems, then the physiotherapist may prescribe upper limb exercises incorporating theraband or free weights for resistance. The physiotherapist will regularly review and modify the optimal intensity and type of exercises for each participant to ensure the intervention remains appropriate and challenging over the study period. We will encourage family members or carers to assist with the exercise program when this is indicated.

Appropriate safe mobility programs will be prescribed if participants have low activity levels, reduced endurance or specific functional goals. Feedback will be provided via monitoring of distance/time or via a pedometer or *FitBit (*internet-linked pedometer). Participants will be encouraged and supported in increasing their physical activity using exercise equipment that they have at home, as well as community physical activity programs (such as Tai Chi or strength and balance classes), community exercise facilities (such as gymnasiums and swimming pools) and a return to past leisure activities such as golf and bowls.

In addition to the interventions targeting the CHS frailty characteristics, individually-tailored intervention will address additional problems identified during assessment. Intervention may include, but will not be limited to, the following examples.

- General health status will be assessed and intervention tailored to each individual's problems. Where indicated, chronic disease management programs will be implemented or reinforced in conjunction with existing health services. We will use the principles of comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and conditions such as incontinence, osteoporosis and impaired cognition. The rehabilitation physician and geriatrician will play a central role in assessment and recommendations for ongoing intervention.
- The rehabilitation physician or geriatrician will review medications used and will discuss any questionable medication use with the participant's general practitioner. Poor compliance with medications will be addressed by initiation or reinforcement of strategies such as education about medications, medication packaging in blister packs and reminder cards.
- Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia, and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and Parkinson's Disease exercise classes.
- The team will refer to agencies that provide assessments and provision of care and services. Examples are the Aged Care Assessment Team for assessment for packages of care, community nursing and service providers.
- If transport is required, we will arrange referral to community transport services, taxi subsidy schemes and mobility parking schemes as appropriate.
- Reduced social interaction will be targeted by facilitating attendance at community-based groups, day centres, clubs and exercise groups, as well as by arranging telephone contact with a volunteer.
- We will advise on meal delivery services and frozen meals if this assistance is needed.
- Mobility aids and other equipment will be recommended, obtained and set up where indicated. This may involve referral to an occupational therapist for environmental

modifications.

- Advice on appropriate footwear will be provided if shoes are suboptimal.
- Ergonomic alterations will be made to optimise home office safety.
- If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program) available in the study area, in addition to the WEBB exercise program. Safety concerns will also be addressed with information about falls prevention, personal alarms and hip protectors.
- If the participant cares for another person or the participant has a carer who needs help, the carer's needs will be assessed and contact with Carers Australia will be suggested.

The physiotherapist and participant will collaborate to set measurable goals within three months of recruitment. The goals will be based upon the CHS frailty characteristics present (such as goals relating to diet, functional consequences of weakness or amount of physical activity), or problems identified during geriatric assessment (such as establishing formal links with a diabetes educator, understanding medications or obtaining a care package). The goals will be documented, reviewed each session by the physiotherapist and participant, and new goals will be set when new issues are targeted.

The physiotherapist will promote adherence to the intervention using strategies including goal setting, a flexible time-frame for intervention delivery, recording of exercise completion, and involvement of family and carers. In addition, programs will be tailored to suit individual requirements and interventions will be designed to be varied, sustainable and enjoyable.

Data collection

Participants will undergo three home-based assessments. The baseline measures will be

assessed prior to randomisation and further assessments will be conducted four and 12 months after randomisation. Additional health service utilisation data will be collected via a telephone call at eight months. Blinded assessors (experienced health professionals) will conduct follow-up assessments. To ensure blinding, participants will be instructed not to disclose group allocation to the assessors. The assessors' perception of group allocation will be assessed, to evaluate the success of assessor blinding.

Outcome measures

Demographic and health information will be collected at baseline. Cognitive function will be assessed with the Mini Mental State Examination.[23]

- *Primary outcomes*

The primary outcomes measured are frailty and mobility, measured at four and 12 months. Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty phenotype evaluates five components of the frailty syndrome and allocates one point for each criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using the lower extremity continuous summary performance score (CSPS),[24] with data collected using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem positions, time taken to walk four metres, and time to rise from a chair and return to the seated position five times.

- *Secondary outcomes*

1. Psychological status will be assessed using the five-item version of the Geriatric Depression Scale.[26]

2. Activities of daily living will be measured using the Barthel Index [27] (100 point version). The mobility component of the Activity Measure for Post Acute Care [28] will measure self reported activity level using Item Response Theory and computer-adaptive testing.
3. Gait speed will be measured using the four-metre walk test.
4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility weights to allow calculation of Quality adjusted life years (QALYs) for use in the economic evaluation.[29]
5. Falls, hospitalisations and admissions to residential aged care facilities will be collected via telephone at four, eight and 12 months and will also be used in the economic analyses.
6. Health and community service use will be recorded at four, eight and 12 months and will be used in economic analyses.

- Additional measures

Adherence measurements will record the acceptance of health and other services by the study participant. The treating physiotherapist will estimate a global level of adherence (in five categories: 0%, <25%, 25-49%, 50-74% and ≥75%) during the 12-month intervention. The treating physiotherapist will evaluate goal attainment in the intervention group using a four-point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal exceeded.

Adverse events will be defined as medical events or injuries arising as a consequence of the trial and resulting in medical attention or restricted activities of daily living for more than two days.[30] Deaths will be documented.

Sample size calculation

An *a priori* power analysis determined 230 participants will need to be recruited, to provide 80% power to detect a clinically and statistically significant 15% between group difference in lower extremity continuous summary performance score (SD = 0.7).[25] This sample size will also provide sufficient power to detect a clinically meaningful 20% between-group difference in transition to frailty. For these calculations, we assumed an α of 0.05, non-compliance of 15% and a dropout rate of 15%.

Statistical analysis

Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable. The other study outcomes will be treated as continuous variables. The effect of group allocation on continuously scored outcome measures at the four month and twelve month follow-ups will be analysed using linear regression models with baseline scores entered into the linear regression models as covariates. To aid interpretation of the change in frailty, frailty will also be reported as a continuous variable. Statistical significance will be set at $P<0.05$ and we will report the differences in percentage or mean (95% confidence interval) between the two groups at the 4-month and 12-month follow-ups.

We will test whether the response to the intervention is modified by the number of frailty criteria present at baseline, by including an interaction term of study groups with number of frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to 74% and ≥75%) on the outcomes in the intervention group at 12-month follow-up. We will examine baseline variables and if there are important between group differences we will adjust for them in the models. The primary analyses will be conducted in accordance with the intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in

the statistical analysis.

Participants will be provided with their own results on request. The overall results will be available to participants once the final results are published. It is anticipated that participants will register their interest in receiving this information when their participation in the study ends.

Economic evaluation

The economic evaluation will be carried out and reported in accordance with health economics reporting standards.[33] The economic evaluation will take the perspective of Australian health and aged care service providers over a 12-month time period. Benefits will be measured in terms of number of transitions to frailty prevented, mobility improvement and QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness analyses will include the cost of delivering the intervention and the cost of health and community service utilisation. Bootstrap sampling will be used to examine the joint probability distribution of costs and outcomes, with the creation of incremental cost-effectiveness planes and cost-effectiveness acceptability curves for each outcome.

Timeframe

Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in October 2015.

DISCUSSION

This trial will provide important information to guide intervention to improve outcomes for older people who are pre-frail. Specifically, it will determine whether a multifactorial interdisciplinary intervention reduces transition to frailty and deterioration in mobility among pre-frail older men and women who live in the community. Frailty and the associated

negative effects such as disability, institutionalisation and hospitalisation are costly to individuals, their families, the health system and society. Despite this cost, to our knowledge there has been no research to date examining the effectiveness of intervention designed to reduce the transition to frailty among pre-frail older people.

The proposed multifactorial intervention will target the needs of each participant based upon the characteristics of frailty present and comprehensive geriatric assessment. The exercise component was designed using evidence from systematic reviews and randomised trials that have demonstrated improved strength, balance and mobility in older people. We will implement strategies to maximise adherence to the intervention, in line with research suggesting good patient adherence increases the effectiveness of health interventions.[7,34] The intervention is based on the program that was feasibly delivered to frail older people in the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to balance, strength and physical activity. Tailoring the exercises to the individual and ongoing reassessment by the treating physiotherapist will ensure safety.

Additional strengths of the study are the generalisability to pre-frail older people and aged care health service settings, and the robust, but pragmatic, clinical trial design. This study uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

This study has some limitations. First, participants cannot be blinded to group allocation, which is a potential source of bias due to possible differential reporting of the weight loss,

activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria, and the co-primary outcome measure (CSPS) are performance-based, which should reduce this bias. Second, as there is no frequency-matched social intervention for the control group, we will not be able to exclude the impact of social aspects of the program on any difference between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the CHS phenotype is the most widely accepted instrument, other validated tools [36] and attention to cognition could be considered in the clinical setting.

If this intervention is shown to be effective, there are major potential benefits to the older population in terms of preventing transition to frailty and improving mobility. Avoiding frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation and institutionalisation, and the associated financial costs. Improved mobility may also result in improved function and better quality of life for older people, their families and carers. If cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of health services. The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

List of abbreviations used

CHS: Cardiovascular Health Study

Pre-FIT: Pre-Frailty Intervention Trial

WEBB: Weight Bearing Exercise for Better Balance

SPPB: Short Physical Performance Battery

SD: standard deviation

QALYs: Quality adjusted life years

CSPS: lower extremity continuous summary performance score

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Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

NF drafted the manuscript. CS, SL, SK and IC are chief investigators on the study. NF, KL, NM, BJ and KH are actively involved in the study. All authors read and approved the final manuscript.

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Figures

Figure 1. Overview of the flow of participants through the Pre-frailty Intervention Trial

Appendix 1. Informed consent form

Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail older people. Study protocol for a randomised controlled trial.

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Key words: frail elderly; randomized controlled trial; therapeutics; exercise.

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ABSTRACT

Introduction: Frailty is a major concern due to its costly and widespread consequences, yet evidence of effective interventions to delay or reduce frailty is lacking. Our previous study found that a multifactorial intervention was feasible and effective in reducing frailty in older people who were already frail. Identifying and treating people in the pre-frail state may be an effective means to preventing or delaying frailty. This study describes a randomised controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on development of frailty in older people who are pre-frail.

Methods and analysis: A single centre, randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis. Two hundred and thirty people aged over 70 who meet the Cardiovascular Health Study frailty criteria for pre-frailty, reside in the community and are without severe cognitive impairment will be recruited. Participants will be randomised to receive a multifactorial intervention or usual care. The intervention group will receive a 12-month interdisciplinary intervention targeting identified characteristics of frailty and problems identified during geriatric assessment. Participants will be followed for a 12-month period. Primary outcome measures will be degree of frailty measured by the number of Cardiovascular Health Study frailty criteria present, and mobility, measured with the Short Physical Performance Battery. Secondary outcomes will include measures of mobility, mood and use of health and community services.

Ethics and dissemination: The study was approved by the Northern Sydney Local Health District Health Research Ethics Committee (1207-213M). The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

Trial Registration: Australian New Zealand Clinical Trials Registry: ACTRN12613000043730.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First randomised controlled trail to evaluate the effectiveness of an intervention on the development of frailty in older people who are pre-frail.

- RSingle centre randomised controlled trial with blinded assessors and intention-to-treat analysis.

- Generalisable to community-dwelling pre-frail older people; there is an objective measure of pre-frailty and minimal exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

- Lack of blinding of participants and staff delivering the intervention due to the nature of the intervention.

INTRODUCTION

Intervention to prevent or delay frailty has important benefits for older people, health services and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by reduced strength, endurance and physiologic function, resulting in increased vulnerability to functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between non-frail and frail. Identifying and treating people in the pre-frail state may be an effective way to prevent or delay frailty.

Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3] which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria, and frail if they meet three or more criteria. The frailty phenotype is predictive of falls, disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have significantly higher risk of developing these adverse outcomes than non-frail people, and frail individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic review found the prevalence of pre-frailty (as defined by the frailty phenotype) in community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is rising globally, the costs associated with frailty will increase in the future. Preventing or delaying frailty has the potential to reduce the burden on individuals and society.

Research into interventions to prevent or reduce frailty is in its infancy. While studies have found that outcomes for frail older people can be improved using multi-factorial interventions such as comprehensive geriatric assessment, and single interventions including exercise

programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome (measured using the frailty phenotype), and found the intervention significantly reduced frailty in frail community-dwelling older people.[7]

Implementing interventions to pre-frail older people may prevent the development of frailty. Older people transition between frailty states,[8] and pre-frail individuals have more than twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to frail is often endues from an acute medical event or a psychological stress exceeding the person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the impact of potential stressors may therefore reduce the risk of becoming frail. Evidence suggests pre-frail older people may respond better to intervention than people who have already moved to a frail state,[10,11] and because pre-frail people have significantly less disability than frail people [3] there is potential for more intensive interventions.

Few trials have identified and targeted pre-frail participants. Previous trials have included samples that are probably pre-frail, for example people at risk of falling,[12] however studies need to have pre-frailty as an inclusion criteria for results to be generalisable to this population. Recent randomised trials [10,13,14] and an observational study [15] have investigated the effects of exercise in people defined as pre-frail using the frailty phenotype; exercise appears to improve function in pre-frail people, however larger studies are needed. To our knowledge, no intervention has been developed to specifically prevent the transition to frailty in pre-frail older people.

We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial that aims to determine whether delivering a multifactorial, interdisciplinary intervention to older people who are pre-frail prevents progression to frailty and improves mobility. We will implement a modification of the intervention previously found to reduce frailty and improve mobility in frail older people [16] to determine whether pre-frail participants receive similar benefits with respect to frailty levels and mobility. To our knowledge this will be the first study to examine the effects of an intervention specifically targeting degree of frailty among older people who are pre-frail. The primary research question is: Does the multifactorial interdisciplinary intervention prevent the progression to frailty (assessed with a frailty phenotype score) and improve mobility among pre-frail older people, when compared with usual care?

METHODS AND DESIGN

Design

A randomised controlled trial will be conducted among 230 participants who are pre-frail. Figure 1 gives an overview of the study design. The Northern Sydney Local Health District Health Research Ethics Committee approved this study (Research Protocol Number 1207-213M) and all participants will give written informed consent prior to randomisation (Appendix 1). The study is registered with the Australia New Zealand Clinical Trials Register ACTRN12613000043730.

Participants

Potential participants will be identified by clinicians working in hospital and community sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-ring-gai Health Service, in Sydney, Australia.

Participants who fulfill the following inclusion criteria will be invited to participate:

1. Male or female, aged 70 years or older
2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)
3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score > 23);

People will be ineligible to participate in the trial if they:

1. Live in a residential aged care facility
2. Have an estimated life expectancy of less than 12 months (estimated by a score of ≤3 on a modified version of the Implicit Illness Severity Scale [18])
3. Currently receive a treatment program from a rehabilitation facility

Table 1.

Characteristic	Criteria
Weight loss/ Shrinking	Self-report of ≥ 4.5 kg lost unintentionally in previous 12 months or loss of ≥5% of weight in prior year by direct measurement of weight
Weakness	Lowest 20% in grip strength, measured using a dynamometer (Saehen Dynamometer, model SH5001). Best of three attempts used. Males scoring 30kg or less, female scoring 18kg or less meet the criteria
Exhaustion	Answering "a moderate amount" or "most of the time" to either of the 2 questions from the Centre for Epidemiological Studies-Depression Scale (CES-D) indicated exhaustion: "How often did you feel that everything you did was an effort in the last week?" or "How often did you feel that you could not get going in the last week?".
Slowness	Time to walk four metres, with or without a walking aid, equals six seconds or more.

Low activity	In the past three months, weight bearing physical activity was not performed, more than four hours per day were spent sitting, and went for a short walk once per month or less.

Randomisation

After consent and completion of the baseline assessment, participants will be entered into the study and randomised to intervention or control groups. Permuted block randomisation will be used,[19] with a random number sequence generated by SPSS v19 and variable block sizes of four and six randomly arranged within blocks of 10. Project personnel not otherwise involved in recruitment or data collection will manage random group allocation. The treatment allocation tables will be stored away from the research office.

Allocation concealment

The research consultant will screen for study eligibility, seek informed consent and conduct the baseline assessment. After baseline assessment is completed, the Research Consultant will telephone the central study office, and the participant will be assigned a participant number and allocated to the control or intervention group. Staff performing the outcome assessment and data analysis will be blinded to group allocation, however due to the nature of the trial it is not possible to blind the participants and staff administering interventions.

Intervention

Participants assigned to the control group will receive the usual care available to older residents of Hornsby Ku-ring-gai area from their general practitioner and community services. At the study site, usual care for non-institutionalised pre-frail older people involves

medical management of health conditions, allied health input, assessment of care needs and provision of care.

Participants in the intervention group will receive an interdisciplinary, multifactorial intervention for one year. The intervention will be individually tailored to each participant based on the following: a) the CHS frailty characteristics present at baseline assessment; b) additional problems identified during a detailed assessment by the physiotherapist providing the intervention program, plus other relevant members of the interdisciplinary team; c) ongoing reassessment by the interdisciplinary team throughout the intervention period. The assessment and intervention will be underpinned by the principles of geriatric evaluation and management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician, a rehabilitation physician, a dietician and a nurse will deliver the intervention. All intervention staff will have experience in delivering interventions to older people. Case management and regular case conferences will assist coordination of the interdisciplinary delivery of the intervention. The treating physiotherapist will have the case coordinator role, liaising with the participant, family, health professionals and service providers, plus coordinating services as indicated.

The intervention will be delivered primarily in participants' homes, with additional community exercise programs and outpatient appointments (for example, podiatrist, memory clinic, continence clinic) offered when indicated.

The interventions targeting the CHS frailty characteristics are described below.

Weight loss

A dietician will evaluate nutritional intake if the participant is not already effectively addressing their recent weight loss. If the participant's body mass index is <18.5 or mid upper arm circumference is < the 10th percentile (using Australian gender and age specific norms), nutritional supplementation will be offered using commercially available, high protein, high energy, supplements. Home delivered meals will be recommended if appropriate clinical criteria apply.

Exhaustion

Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale score is high. Where the participant is socially isolated, opportunities to encourage greater social engagement will be identified, e.g. day activity groups, physical activity programs in the community, and telephone contact with volunteers.

Grip weakness, slow four metre walk time, or low physical activity level

A physiotherapist experienced in aged care will visit the participant's home ten times in the 12 months study period. There will be five sessions in the first three months after randomisation, and five sessions over the following nine months. Visits will be 60 to 120 minutes duration. The physiotherapist will prescribe a home exercise program to be performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree of difficulty and number of repetitions prescribed will be based upon assessment of the individual participant's abilities. Lower limb balance and strengthening exercises will utilise the Weight Bearing Exercise for Better Balance (WEBB) program, available at www.webb.org.au.[22] The program targets strength and control of the lower limb extensor muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a

wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as appropriate. Balance will be targeted with exercises performed in standing with a progressively narrowed base (feet together, tandem stance, single leg stance), stepping, walking and reaching. Upper limb support will be minimised in order to adequately challenge balance, but to ensure safety the environment will be set up with stable supports (e.g. bench or table) close by that can be held as necessary. In addition, if upper limb weakness is creating functional problems, then the physiotherapist may prescribe upper limb exercises incorporating theraband or free weights for resistance. The physiotherapist will regularly review and modify the optimal intensity and type of exercises for each participant to ensure the intervention remains appropriate and challenging over the study period. We will encourage family members or carers to assist with the exercise program when this is indicated.

Appropriate safe mobility programs will be prescribed if participants have low activity levels, reduced endurance or specific functional goals. Feedback will be provided via monitoring of distance/time or via a pedometer or *FitBit (*internet-linked pedometer). Participants will be encouraged and supported in increasing their physical activity using exercise equipment that they have at home, as well as community physical activity programs (such as Tai Chi or strength and balance classes), community exercise facilities (such as gymnasiums and swimming pools) and a return to past leisure activities such as golf and bowls.

In addition to the interventions targeting the CHS frailty characteristics, individually-tailored intervention will address additional problems identified during assessment. Intervention may include, but will not be limited to, the following examples.

- General health status will be assessed and intervention tailored to each individual's problems. Where indicated, chronic disease management programs will be implemented or reinforced in conjunction with existing health services. We will use the principles of comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and conditions such as incontinence, osteoporosis and impaired cognition. The rehabilitation physician and geriatrician will play a central role in assessment and recommendations for ongoing intervention.
- The rehabilitation physician or geriatrician will review medications used and will discuss any questionable medication use with the participant's general practitioner. Poor compliance with medications will be addressed by initiation or reinforcement of strategies such as education about medications, medication packaging in blister packs and reminder cards.
- Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia, and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and Parkinson's Disease exercise classes.
- The team will refer to agencies that provide assessments and provision of care and services. Examples are the Aged Care Assessment Team for assessment for packages of care, community nursing and service providers.
- If transport is required, we will arrange referral to community transport services, taxi subsidy schemes and mobility parking schemes as appropriate.
- Reduced social interaction will be targeted by facilitating attendance at community-based groups, day centres, clubs and exercise groups, as well as by arranging telephone contact with a volunteer.
- We will advise on meal delivery services and frozen meals if this assistance is needed.
- Mobility aids and other equipment will be recommended, obtained and set up where indicated. This may involve referral to an occupational therapist for environmental

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modifications.

- Advice on appropriate footwear will be provided if shoes are suboptimal.
- Ergonomic alterations will be made to optimise home office safety.
- If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program) available in the study area, in addition to the WEBB exercise program. Safety concerns will also be addressed with information about falls prevention, personal alarms and hip protectors.
- If the participant cares for another person or the participant has a carer who needs help, the carer's needs will be assessed and contact with Carers Australia will be suggested.

The physiotherapist and participant will collaborate to set measurable goals within three months of recruitment. The goals will be based upon the CHS frailty characteristics present (such as goals relating to diet, functional consequences of weakness or amount of physical activity), or problems identified during geriatric assessment (such as establishing formal links with a diabetes educator, understanding medications or obtaining a care package). The goals will be documented, reviewed each session by the physiotherapist and participant, and new goals will be set when new issues are targeted.

The physiotherapist will promote adherence to the intervention using strategies including goal setting, a flexible time-frame for intervention delivery, recording of exercise completion, and involvement of family and carers. In addition, programs will be tailored to suit individual requirements and interventions will be designed to be varied, sustainable and enjoyable.

Data collection

Participants will undergo three home-based assessments. The baseline measures will be

assessed prior to randomisation and further assessments will be conducted four and 12 months after randomisation. Additional health service utilisation data will be collected via a telephone call at eight months. Blinded assessors (experienced health professionals) will conduct follow-up assessments. To ensure blinding, participants will be instructed not to disclose group allocation to the assessors. The assessors' perception of group allocation will be assessed, to evaluate the success of assessor blinding.

Outcome measures

Demographic and health information will be collected at baseline. Cognitive function will be assessed with the Mini Mental State Examination.[23]

- *Primary outcomes*

The primary outcomes measured are frailty and mobility, measured at four and 12 months. Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty phenotype evaluates five components of the frailty syndrome and allocates one point for each criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using the lower extremity continuous summary performance score (CSPS),[24] with data collected using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem positions, time taken to walk four metres, and time to rise from a chair and return to the seated position five times.

- *Secondary outcomes*

1. Psychological status will be assessed using the five-item version of the Geriatric Depression Scale.[26]

2. Activities of daily living will be measured using the Barthel Index [27] (100 point version). The mobility component of the Activity Measure for Post Acute Care [28] will measure self reported activity level using Item Response Theory and computer-adaptive testing.
3. Gait speed will be measured using the four-metre walk test.
4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility weights to allow calculation of Quality adjusted life years (QALYs) for use in the economic evaluation.[29]
5. Falls, hospitalisations and admissions to residential aged care facilities will be collected via telephone at four, eight and 12 months and will also be used in the economic analyses.
6. Health and community service use will be recorded at four, eight and 12 months and will be used in economic analyses.

- *Additional measures*

Adherence measurements will record the acceptance of health and other services by the study participant. The treating physiotherapist will estimate a global level of adherence (in five categories: 0%, <25%, 25-49%, 50-74% and ≥75%) during the 12-month intervention. The treating physiotherapist will evaluate goal attainment in the intervention group using a four-point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal exceeded.

Adverse events will be defined as medical events or injuries arising as a consequence of the trial and resulting in medical attention or restricted activities of daily living for more than two days.[30] Deaths will be documented.

Sample size calculation

An *a priori* power analysis determined 230 participants will need to be recruited, to provide 80% power to detect a clinically and statistically significant 15% between group difference in lower extremity continuous summary performance score (SD = 0.7).[25] This sample size will also provide sufficient power to detect a clinically meaningful 20% between-group difference in transition to frailty. For these calculations, we assumed an α of 0.05, non-compliance of 15% and a dropout rate of 15%.

Statistical analysis

Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable. The other study outcomes will be treated as continuous variables. The effect of group allocation on continuously scored outcome measures at the four month and twelve month follow-ups will be analysed using linear regression models with baseline scores entered into the linear regression models as covariates. To aid interpretation of the change in frailty, frailty will also be reported as a continuous variable. Statistical significance will be set at $P<0.05$ and we will report the differences in percentage or mean (95% confidence interval) between the two groups at the 4-month and 12-month follow-ups.

We will test whether the response to the intervention is modified by the number of frailty criteria present at baseline, by including an interaction term of study groups with number of frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to 74% and ≥75%) on the outcomes in the intervention group at 12-month follow-up. We will examine baseline variables and if there are important between group differences we will adjust for them in the models. The primary analyses will be conducted in accordance with the intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in

the statistical analysis.

Participants will be provided with their own results on request. The overall results will be available to participants once the final results are published. It is anticipated that participants will register their interest in receiving this information when their participation in the study ends.

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Economic evaluation

The economic evaluation will be carried out and reported in accordance with health economics reporting standards.[33] The economic evaluation will take the perspective of Australian health and aged care service providers over a 12-month time period. Benefits will be measured in terms of number of transitions to frailty prevented, mobility improvement and QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness analyses will include the cost of delivering the intervention and the cost of health and community service utilisation. Bootstrap sampling will be used to examine the joint probability distribution of costs and outcomes, with the creation of incremental cost-effectiveness planes and cost-effectiveness acceptability curves for each outcome.

Timeframe

Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in October 2015.

DISCUSSION

This trial will provide important information to guide intervention to improve outcomes for older people who are pre-frail. Specifically, it will determine whether a multifactorial interdisciplinary intervention reduces transition to frailty and deterioration in mobility among

pre-frail older men and women who live in the community. Frailty and the associated negative effects such as disability, institutionalisation and hospitalisation are costly to individuals, their families, the health system and society. Despite this cost, to our knowledge there has been no research to date examining the effectiveness of intervention designed to reduce the transition to frailty among pre-frail older people.

The proposed multifactorial intervention will target the needs of each participant based upon the characteristics of frailty present and comprehensive geriatric assessment. The exercise component was designed using evidence from systematic reviews and randomised trials that have demonstrated improved strength, balance and mobility in older people. We will implement strategies to maximise adherence to the intervention, in line with research suggesting good patient adherence increases the effectiveness of health interventions.[7,34] The intervention is based on the program that was feasibly delivered to frail older people in the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to balance, strength and physical activity. Tailoring the exercises to the individual and ongoing reassessment by the treating physiotherapist will ensure safety.

Additional strengths of the study are the generalisability to pre-frail older people and aged care health service settings, and the robust, but pragmatic, clinical trial design. This study uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion criteria. The intervention being examined is readily transferable to routine clinical practice in the aged care health service setting and the interdisciplinary approach is relevant to several professional groups in aged care.

This study has some limitations. First, participants cannot be blinded to group allocation,

which is a potential source of bias due to possible differential reporting of the weight loss, activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria, and the co-primary outcome measure (CSPS) are performance-based, which should reduce this bias. Second, as there is no frequency-matched social intervention for the control group, we will not be able to exclude the impact of social aspects of the program on any difference between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the CHS phenotype is the most widely accepted instrument, other validated tools [36] and attention to cognition could be considered in the clinical setting.

If this intervention is shown to be effective, there are major potential benefits to the older population in terms of preventing transition to frailty and improving mobility. Avoiding frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation and institutionalisation, and the associated financial costs. Improved mobility may also result in improved function and better quality of life for older people, their families and carers. If cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of health services. The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

List of abbreviations used

CHS: Cardiovascular Health Study

Pre-FIT: Pre-Frailty Intervention Trial

WEBB: Weight Bearing Exercise for Better Balance

SPPB: Short Physical Performance Battery

SD: standard deviation

QALYs: Quality adjusted life years

CSPS: lower extremity continuous summary performance score

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Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

NF drafted the manuscript. All authors are actively involved in the study. All authors read and approved the final manuscript.

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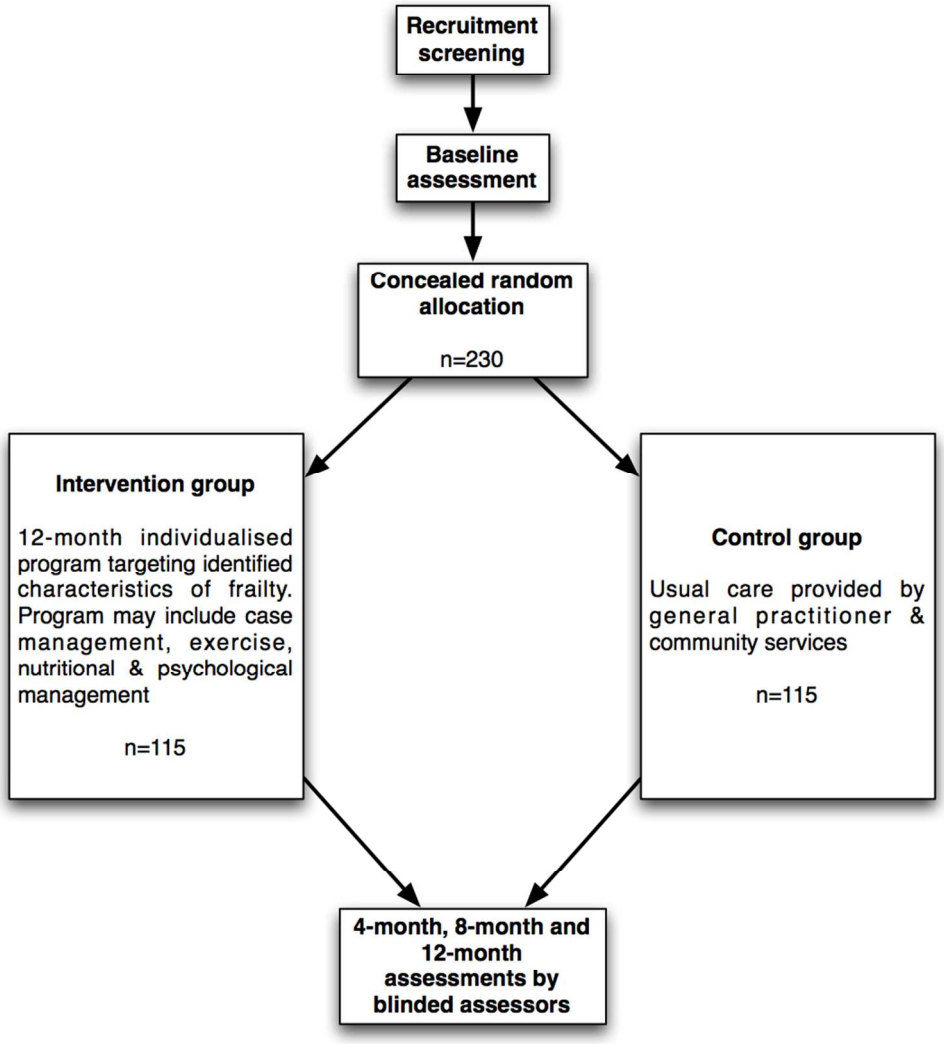
583 **Figures**

584 **Figure 1.** Overview of the flow of participants through the Pre-frailty Intervention Trial

585 **Appendix 1.** Informed consent form

586



Overview of the flow of participants through the Pre-frailty Intervention Trial
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Health
Northern Sydney
Local Health District

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

Invitation
You are invited to participate in a research study investigating the effectiveness of a specialised treatment program for older people who are pre-frail.

The study is being conducted by Hornsby Ku-ring-gai Hospital and the Rehabilitation Studies Unit (University of Sydney).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the purpose of this study?
The purpose is to investigate whether or not a program involving contact with one or several health professionals over a period of approximately 12 months is effective in improving the overall health of people who are pre-frail. The study definition of pre-frail requires that participants have one or two criteria that have been linked to frailty in a previous study (The Cardiovascular Health Study). These criteria are: 1. Unexplained weight loss in the past year. 2. Diminished grip strength. 3. Self reported exhaustion. 4. Sow gait speed and 5. low energy expenditure.

2. Why have I been invited to participate in this study?
You are eligible to participate in this study because you are aged over 70 years, and may meet our definition of being pre-frail.

3. What if I don't want to take part in this study or if I want to withdraw later?
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect any treatment you receive now or in the future. Whatever your decision, it will not affect any future relationship with Hornsby Hospital or The University of Sydney.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

4. What are the alternatives to participating in this study?

If you decide not to participate in this study, you will still receive the standard treatment and care as would otherwise normally have been available to you in this area, generally accessible following consultation with your general practitioner.

5. What does this study involve?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form attached to this information sheet.

This study will be conducted over a period of 12 months.

This project is a randomised trial. If you agree to participate you will be put into one of two groups. One group will receive the multifactorial intervention while the other group will receive the 'usual care' that would otherwise have been available to them. Both groups will receive visits from our research team over a12 month period. The results will be compared to see whether one treatment is more effective than the other. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the researcher nor the study participant can decide which group the participant will be allocated to. You will be told which group you are in.

All participants will be asked to complete three assessments with a study research nurse. One assessment is conducted at the commencement of the study, one after four months and the final assessment at the end of your involvement with the study (at 12 months). These assessments involve some minor strength and balance testing and some questions about your health, well being and service usage.

In addition, the researchers may require access to your hospital medical records in order
to obtain information relevant to the study.

6. How is this study being paid for?

The study is being sponsored by a trust fund connected to the Rehabilitation and Aged Care Service at Hornsby Ku-ring-gai Hospital. No money (besides normal salary) is paid directly to any individual researchers.

7. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, it is possible you could develop a medical complication from participating in this study. Based on our experience there is a small risk that a

musculoskeletal symptom may develop as a result of the physical therapy intervention. This could be in the form of a muscular strain, or minor stress to ligaments or joint. In this unlikely event, the exercise program will be modified. There is also a slight risk of falling while exercising and this possibility will also be monitored.

8. What happens if I suffer injury or complications as a result of the study?
If you suffer any injuries or complications as a result of this study, you should contact the researcher visiting you as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the project intervention or by the negligence of any of the research staff who visit you. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

9. Will I benefit from the study?
This study aims to further develop medical knowledge and may improve future treatment of frailty; it may or may not be of direct benefit you.

10. Will taking part in this study cost me anything, and will I be paid?
Participation in this study will not cost you anything; neither will you be paid for your participation.

11. How will my confidentiality be protected?
Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or as required by law. Only the study researchers will have access to your details and results and all information will be held securely at Hornsby Ku-ring-gai Hospital.

12. What happens with the results?
If you give us your permission by signing the consent document, we plan to publish the results of the study in peer reviewed journals at the conclusion of the trial. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. What happens to my treatment when the study is finished?
If you are allocated to the group receiving the intervention, these visits will cease at the end of the study period. Usual community care, assessable through your general practitioner will resume at this point.

14. What should I do if I want to discuss this study further before I decide?
When you have read this information, the research nurse will discuss it with you and address any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her or any member of the project team.

15. Who should I contact if I have concerns about the conduct of this study?
This study has been approved by the Northern Sydney Coast Human Research ethics Committee of Northern Sydney and Central Coast Local Health Districts (NSLHD & CCLHD). Any person with concerns or complaints about the conduct of this study should contact Professor Ian Cameron at the Rehabilitation Studies Unit on (02) 9808-9236 or alternatively the Research Office on (02) 9926 8106 and quote " The Pre-frailty Intervention Trial" (Pre-FIT).

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

1. I,.....

   of.....

   ……

   agree to participate as a subject in the study described in the attached participant information statement : **Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail.**

2. I acknowledge that I have read the participant information statement, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

4. I understand that I can withdraw from the study at any time without prejudice to my relationship to the University of Sydney or Hornsby Ku-ring-gai Hospital Health Service.

5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

6. I understand that if I have any questions relating to my participation in this research, I may contact Professor Ian Cameron on telephone (02) 9808-9236 who will be happy to answer them.

7. I give my consent for my hospital records to be accessed for the purposes of this research if necessary.

8. I acknowledge receipt of a copy of this Consent Form and the Participant Information Statement.

I understand that should I have a complaint in regards to the conduct of this trial it may be directed to either Professor Ian Cameron on telephone (02) 9808-9236 or the Northern Sydney Coast Human Research Ethics Committee on (02) 9926 8106.

Signature of subject	**Please PRINT name**	**Date**

Signature of Researcher	**Please PRINT name**	**Date**

Health
Northern Sydney
Local Health District

NSW GOVERNMENT

Hornby Ku-ring-gai Health Service

Pre-FIT: A multifactorial interdisciplinary treatment program for older people who are pre-frail

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the University of Sydney or Hornsby Ku-ring-gai Hospital

Signature……..…….. Date…../…../…..

Please PRINT Name:……

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	5,6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	11,12
Objectives	7	Specific objectives or hypotheses	9

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16,18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17,18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16,17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19,20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19,20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.