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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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3 1 **Effectiveness of a multifactorial intervention on preventing development of frailty in**  
4 2 **pre-frail older people. Study protocol for a randomised controlled trial.**  
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50 48 **Key words:** frail elderly; randomized controlled trial; therapeutics; exercise.  
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53 51  
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3 50 **ABSTRACT**  
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52 **Introduction:** Frailty is a major concern due to its costly and widespread consequences, yet  
53 evidence of effective interventions to delay or reduce frailty is lacking. Our previous study  
54 found that a multifactorial intervention was feasible and effective in reducing frailty in older  
55 people who were already frail. Identifying and treating people in the pre-frail state may be an  
56 effective means to preventing or delaying frailty. This study describes a randomised  
57 controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on  
58 development of frailty in older people who are pre-frail.

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

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

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73 **Trial Registration:** Australian New Zealand Clinical Trials Registry:

74 ACTRN12613000043730.

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For peer review only

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3 76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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6 77     ▪ First randomised controlled trial to evaluate the effectiveness of an intervention on the  
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8 78         development of frailty in older people who are pre-frail.  
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13 80     ▪ Single centre randomised controlled trial with blinded assessors and intention-to-treat  
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15 81         analysis.  
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19 83     ▪ Generalisable to community-dwelling pre-frail older people; there is an objective  
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21 84         measure of pre-frailty and minimal exclusion criteria. The intervention being  
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23 85         examined is readily transferable to routine clinical practice in the aged care health  
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25 86         service setting and the interdisciplinary approach is relevant to several professional  
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27 87         groups in aged care.  
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32 89     ▪ Lack of blinding of participants and staff delivering the intervention due to the nature  
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34 90         of the intervention.  
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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 and Trust Fund
Primary sponsor	Doris Whiting Special Purpose and Trust Fund
Secondary sponsor(s)	
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Contact for scientific queries	Professor Ian Cameron, <a href="mailto:ian.cameron@sydney.edu.au">ian.cameron@sydney.edu.au</a> , phone +61 299264962, Rehabilitation Studies Unit, Level 13, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW 2065.
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)	<p>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.</p> <p>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.</p>
Key inclusion and exclusion	Ages eligible for study: $\geq 70$ years

criteria	<p>Sexes eligible for study: both</p> <p>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)</p> <p>Exclusion criteria:  Living in a residential aged care facility  Have an estimated life expectancy of less than 12 months (estimated by a score of <math>\leq 3</math> on a modified version of the Implicit Illness Severity Scale)  Currently receiving a treatment program from a rehabilitation facility</p>
Study type	<p>Interventional  Allocation: randomised  Intervention model: parallel assignment  Masking: single blind (outcome assessor)  Primary purpose: prevention</p>
Date of first enrolment	14 January 2013
Target sample size	230
Recruitment status	Recruitment completed 07 October 2014
Primary outcome(s)	<p>Pre frailty (which is the presence of one or two of the five Cardiovascular Health Study frailty criteria)  Short Physical Performance Battery</p>
Key secondary outcomes	<p>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.</p>

92 Date: 2 November 2015, Version 1.

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3 94 **INTRODUCTION**  
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6 95 Intervention to prevent or delay frailty has important benefits for older people, health services  
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8 96 and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by  
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10 97 reduced strength, endurance and physiologic function, resulting in increased vulnerability to  
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12 98 functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between  
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14 99 non-frail and frail. Identifying and treating people in the pre-frail state may be an effective  
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16 100 way to prevent or delay frailty.  
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20 101

21 102 Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3]  
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23 103 which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and  
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25 104 slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People  
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27 105 are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria,  
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29 106 and frail if they meet three or more criteria. The frailty phenotype is predictive of falls,  
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31 107 disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have  
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33 108 significantly higher risk of developing these adverse outcomes than non-frail people, and frail  
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35 109 individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic  
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37 110 review found the prevalence of pre-frailty (as defined by the frailty phenotype) in  
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39 111 community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the  
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41 112 prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is  
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43 113 rising globally, the costs associated with frailty will increase in the future. Preventing or  
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45 114 delaying frailty has the potential to reduce the burden on individuals and society.  
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52 116 Research into interventions to prevent or reduce frailty is in its infancy. While studies have  
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54 117 found that outcomes for frail older people can be improved using multi-factorial interventions  
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56 118 such as comprehensive geriatric assessment, and single interventions including exercise  
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3 119 programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of  
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5 120 intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the  
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7 121 effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome  
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10 122 (measured using the frailty phenotype), and found the intervention significantly reduced  
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12 123 frailty in frail community-dwelling older people.[7]

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16 125 Implementing interventions to pre-frail older people may prevent the development of frailty.  
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18 126 Older people transition between frailty states,[8] and pre-frail individuals have more than  
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20 127 twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to  
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22 128 frail is often endues from an acute medical event or a psychological stress exceeding the  
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24 129 person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the  
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26 130 impact of potential stressors may therefore reduce the risk of becoming frail. Evidence  
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28 131 suggests pre-frail older people may respond better to intervention than people who have  
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30 132 already moved to a frail state,[10,11] and because pre-frail people have significantly less  
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32 133 disability than frail people [3] there is potential for more intensive interventions.

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38 135 Few trials have identified and targeted pre-frail participants. Previous trials have included  
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40 136 samples that are probably pre-frail, for example people at risk of falling,[12] however studies  
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42 137 need to have pre-frailty as an inclusion criteria for results to be generalisable to this  
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44 138 population. Recent randomised trials [10,13,14] and an observational study [15] have  
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46 139 investigated the effects of exercise in people defined as pre-frail using the frailty phenotype;  
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48 140 exercise appears to improve function in pre-frail people, however larger studies are needed.  
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50 141 To our knowledge, no intervention has been developed to specifically prevent the transition  
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52 142 to frailty in pre-frail older people.

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3 144 We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial  
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5 145 that aims to determine whether delivering a multifactorial, interdisciplinary intervention to  
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7 146 older people who are pre-frail prevents progression to frailty and improves mobility. We will  
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10 147 implement a modification of the intervention previously found to reduce frailty and improve  
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12 148 mobility in frail older people [16] to determine whether pre-frail participants receive similar  
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14 149 benefits with respect to frailty levels and mobility. To our knowledge this will be the first  
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16 150 study to examine the effects of an intervention specifically targeting degree of frailty among  
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18 151 older people who are pre-frail. The primary research question is: Does the multifactorial  
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21 152 interdisciplinary intervention prevent the progression to frailty (assessed with a frailty  
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23 153 phenotype score) and improve mobility among pre-frail older people, when compared with  
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25 154 usual care?  
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## 30 156 **METHODS AND DESIGN**

### 31 32 157 **Design**

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34 158 A single-centre, randomised controlled trial will be conducted among 230 participants who  
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36 159 are pre-frail. Figure 1 gives an overview of the study design. The Northern Sydney Local  
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38 160 Health District Health Research Ethics Committee approved this study (Research Protocol  
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40 161 Number 1207-213M) and all participants will give written informed consent prior to  
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42 162 randomisation (Appendix 1). The study is registered with the Australia New Zealand Clinical  
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44 163 Trials Register ACTRN12613000043730.  
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### 49 165 **Participants**

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52 166 Potential participants will be identified by clinicians working in hospital and community  
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54 167 sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-  
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56 168 ring-gai Health Service, in Sydney, Australia.  
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170 Participants who fulfill the following inclusion criteria will be invited to participate:

- 171 1. Male or female, aged 70 years or older
- 172 2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)
- 173 3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score >
- 174 23);

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

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

181 Table 1.

Characteristic	Criteria
Weight loss/ Shrinking	Self-report of $\geq 4.5$ kg lost unintentionally in previous 12 months or loss of $\geq 5\%$ of weight in prior year by direct measurement of weight
Weakness	Lowest 20% in grip strength, measured using a dynamometer (Saehan 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.
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**183 Randomisation**

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

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**191 Allocation concealment**

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

198

**199 Intervention**

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

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3 203 medical management of health conditions, allied health input, assessment of care needs and  
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5 204 provision of care.  
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10 206 Participants in the intervention group will receive an interdisciplinary, multifactorial  
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12 207 intervention for one year. The intervention will be individually tailored to each participant  
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14 208 based on the following: a) the CHS frailty characteristics present at baseline assessment; b)  
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16 209 additional problems identified during a detailed assessment by the physiotherapist providing  
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18 210 the intervention program, plus other relevant members of the interdisciplinary team; c)  
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20 211 ongoing reassessment by the interdisciplinary team throughout the intervention period. The  
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22 212 assessment and intervention will be underpinned by the principles of geriatric evaluation and  
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24 213 management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician,  
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26 214 a rehabilitation physician, a dietician and a nurse will deliver the intervention. All  
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28 215 intervention staff will have experience in delivering interventions to older people. Case  
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30 216 management and regular case conferences will assist coordination of the interdisciplinary  
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32 217 delivery of the intervention. The treating physiotherapist will have the case coordinator role,  
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34 218 liaising with the participant, family, health professionals and service providers, plus  
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36 219 coordinating services as indicated.  
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43 221 The intervention will be delivered primarily in participants' homes, with additional  
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45 222 community exercise programs and outpatient appointments (for example, podiatrist, memory  
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47 223 clinic, continence clinic) offered when indicated.  
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52 225 The interventions targeting the CHS frailty characteristics are described below.  
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3 227 *Weight loss*

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5 228 A dietician will evaluate nutritional intake if the participant is not already effectively  
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7 229 addressing their recent weight loss. If the participant's body mass index is <18.5 or mid  
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9 230 upper arm circumference is < the 10<sup>th</sup> percentile (using Australian gender and age specific  
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11 231 norms), nutritional supplementation will be offered using commercially available, high  
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13 232 protein, high energy, supplements. Home delivered meals will be recommended if  
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15 233 appropriate clinical criteria apply.  
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22 235 *Exhaustion*

23 236 Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale  
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25 237 score is high. Where the participant is socially isolated, opportunities to encourage greater  
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27 238 social engagement will be identified, e.g. day activity groups, physical activity programs in  
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29 239 the community, and telephone contact with volunteers.  
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34 241 *Grip weakness, slow four metre walk time, or low physical activity level*

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36 242 A physiotherapist experienced in aged care will visit the participant's home ten times in the  
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38 243 12 months study period. There will be five sessions in the first three months after  
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40 244 randomisation, and five sessions over the following nine months. Visits will be 60 to 120  
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42 245 minutes duration. The physiotherapist will prescribe a home exercise program to be  
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44 246 performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree  
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46 247 of difficulty and number of repetitions prescribed will be based upon assessment of the  
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48 248 individual participant's abilities. Lower limb balance and strengthening exercises will utilise  
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50 249 the Weight Bearing Exercise for Better Balance (WEBB) program, available at  
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52 250 [www.webb.org.au](http://www.webb.org.au).<sup>[22]</sup> The program targets strength and control of the lower limb extensor  
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54 251 muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up  
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56 252 from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a  
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3 253 wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as  
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5 254 appropriate. Balance will be targeted with exercises performed in standing with a  
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7 255 progressively narrowed base (feet together, tandem stance, single leg stance), stepping,  
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10 256 walking and reaching. Upper limb support will be minimised in order to adequately challenge  
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12 257 balance, but to ensure safety the environment will be set up with stable supports (e.g. bench  
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14 258 or table) close by that can be held as necessary. In addition, if upper limb weakness is  
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16 259 creating functional problems, then the physiotherapist may prescribe upper limb exercises  
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18 260 incorporating theraband or free weights for resistance. The physiotherapist will regularly  
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21 261 review and modify the optimal intensity and type of exercises for each participant to ensure  
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23 262 the intervention remains appropriate and challenging over the study period. We will  
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25 263 encourage family members or carers to assist with the exercise program when this is  
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27 264 indicated.  
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32 266 Appropriate safe mobility programs will be prescribed if participants have low activity levels,  
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34 267 reduced endurance or specific functional goals. Feedback will be provided via monitoring of  
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36 268 distance/time or via a pedometer or *FitBit* (internet-linked pedometer). Participants will be  
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38 269 encouraged and supported in increasing their physical activity using exercise equipment that  
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40 270 they have at home, as well as community physical activity programs (such as Tai Chi or  
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42 271 strength and balance classes), community exercise facilities (such as gymnasiums and  
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44 272 swimming pools) and a return to past leisure activities such as golf and bowls.  
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49 274 In addition to the interventions targeting the CHS frailty characteristics, individually-tailored  
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51 275 intervention will address additional problems identified during assessment. Intervention may  
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53 276 include, but will not be limited to, the following examples.  
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3 278 • General health status will be assessed and intervention tailored to each individual's  
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5 279 problems. Where indicated, chronic disease management programs will be implemented  
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7 280 or reinforced in conjunction with existing health services. We will use the principles of  
8  
9 281 comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and  
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11 282 conditions such as incontinence, osteoporosis and impaired cognition.  
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14 283 • The rehabilitation physician or geriatrician will review medications used and will discuss  
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16 284 any questionable medication use with the participant's general practitioner. Poor  
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18 285 compliance with medications will be addressed by initiation or reinforcement of strategies  
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20 286 such as education about medications, medication packaging in blister packs and reminder  
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22 287 cards.  
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25 288 • Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia,  
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27 289 and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and  
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29 290 Parkinson's Disease exercise classes.  
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32 291 • The team will refer to agencies that provide assessments and provision of care and  
33  
34 292 services. Examples are the Aged Care Assessment Team for assessment for packages of  
35  
36 293 care, community nursing and service providers.  
37  
38  
39 294 • If transport is required, we will arrange referral to community transport services, taxi  
40  
41 295 subsidy schemes and mobility parking schemes as appropriate.  
42  
43 296 • Reduced social interaction will be targeted by facilitating attendance at community-based  
44  
45 297 groups, day centres, clubs and exercise groups, as well as by arranging telephone contact  
46  
47 298 with a volunteer.  
48  
49 299 • We will advise on meal delivery services and frozen meals if this assistance is needed.  
50  
51 300 • Mobility aids and other equipment will be recommended, obtained and set up where  
52  
53 301 indicated. This may involve referral to an occupational therapist for environmental  
54  
55 302 modifications.  
56  
57  
58 303 • Advice on appropriate footwear will be provided if shoes are suboptimal.  
59  
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3 304 • Ergonomic alterations will be made to optimise home office safety.  
4  
5 305 • If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls  
6  
7 306 and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program)  
8  
9 307 available in the study area, in addition to the WEBB exercise program. Safety concerns  
10  
11 308 will also be addressed with information about falls prevention, personal alarms and hip  
12  
13 309 protectors.  
14  
15 310 • If the participant cares for another person or the participant has a carer who needs help,  
16  
17 311 the carer's needs will be assessed and contact with Carers Australia will be suggested.  
18  
19  
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22

23 313 The physiotherapist and participant will collaborate to set measurable goals within three  
24  
25 314 months of recruitment. The goals will be based upon the CHS frailty characteristics present  
26  
27 315 (such as goals relating to diet, functional consequences of weakness or amount of physical  
28  
29 316 activity), or problems identified during geriatric assessment (such as establishing formal links  
30  
31 317 with a diabetes educator, understanding medications or obtaining a care package). The goals  
32  
33 318 will be documented, reviewed each session by the physiotherapist and participant, and new  
34  
35 319 goals will be set when new issues are targeted.  
36  
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40  
41 321 The physiotherapist will promote adherence to the intervention using strategies including  
42  
43 322 goal setting, a flexible time-frame for intervention delivery, recording of exercise completion,  
44  
45 323 and involvement of family and carers. In addition, programs will be tailored to suit individual  
46  
47 324 requirements and safety concerns, and interventions will be designed to be varied, sustainable  
48  
49 325 and enjoyable.  
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52 326

### 53 327 **Data collection**

54  
55  
56 328 Participants will undergo three home-based assessments. The baseline measures will be  
57  
58 329 assessed prior to randomisation and further assessments will be conducted four and 12  
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3 330 months after randomisation. Additional health service utilisation data will be collected via a  
4  
5 331 telephone call at eight months. Blinded assessors (experienced health professionals, trained in  
6  
7 332 conducting the outcome measures) will conduct follow-up assessments. To ensure blinding,  
8  
9  
10 333 participants will be instructed not to disclose group allocation to the assessors. The assessors'  
11  
12 334 perception of group allocation will be assessed, to evaluate the success of assessor blinding.  
13  
14 335 The data collection forms are available from the authors. Personal information and data will  
15  
16 336 be collated on paper forms and entered in a Microsoft Access using range checks for data  
17  
18 337 values. Paper files will be stored in a locked filing cabinet and electronic information will be  
19  
20  
21 338 stored in a password protected computer. The research documents will be kept for at least 5  
22  
23 339 years after study completion. The final trial dataset will be available to trial authors who are  
24  
25 340 undertaking data analysis for presentations or publications.  
26  
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341

**342 Outcome measures**

31  
32 343 Demographic and health information will be collected at baseline. Cognitive function will be  
33  
34 344 assessed with the Mini Mental State Examination.[23]  
35

345

**346 - Primary outcomes**

37  
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39  
40 347 The primary outcomes measured are frailty and mobility, measured at four and 12 months.  
41  
42 348 Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty  
43  
44 349 phenotype evaluates five components of the frailty syndrome and allocates one point for each  
45  
46 350 criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are  
47  
48 351 defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using  
49  
50 352 the lower extremity continuous summary performance score (CSPS),[24] with data collected  
51  
52 353 using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability  
53  
54 354 to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem  
55  
56 355 positions, time taken to walk four metres, and time to rise from a chair and return to the  
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3 356 seated position five times.  
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8 358 - *Secondary outcomes*

9  
10 359 1. Psychological status will be assessed using the five-item version of the Geriatric

11 360 Depression Scale.[26]

12  
13 361 2. Activities of daily living will be measured using the Barthel Index [27] (100 point

14 362 version). The mobility component of the Activity Measure for Post Acute Care [28] will

15 363 measure self reported activity level using Item Response Theory and computer-adaptive

16 364 testing.

17 365 3. Gait speed will be measured using the four-metre walk test.

18 366 4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility

19 367 weights to allow calculation of Quality adjusted life years (QALYs) for use in the

20 368 economic evaluation.[29]

21 369 5. Falls, hospitalisations and admissions to residential aged care facilities will be collected

22 370 via telephone at four, eight and 12 months and will also be used in the economic analyses.

23 371 6. Health and community service use will be recorded at four, eight and 12 months and will

24 372 be used in economic analyses.

25 373

26 374 - *Additional measures*

27 375 Adherence measurements will record the acceptance of health and other services by the study

28 376 participant. The treating physiotherapist will estimate a global level of adherence (in five

29 377 categories: 0%, <25%, 25-49%, 50-74% and  $\geq 75\%$ ) during the 12-month intervention. The

30 378 treating physiotherapist will evaluate goal attainment in the intervention group using a four-

31 379 point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal

32 380 exceeded.

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3 382 Adverse events will be defined as medical events or injuries arising as a consequence of the  
4  
5 383 trial and resulting in medical attention or restricted activities of daily living for more than two  
6  
7 384 days.[30] Deaths will be documented. The intervention staff will report adverse events and  
8  
9  
10 385 deaths to the Chief Investigator within two days and they will be discussed at the next case  
11  
12 386 conference.

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### 15 16 388 **Sample size calculation**

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18 389 An *a priori* power analysis determined 230 participants will need to be recruited, to provide  
19  
20  
21 390 80% power to detect a clinically and statistically significant 15% between group difference in  
22  
23 391 lower extremity continuous summary performance score (SD = 0.7).[25] This sample size  
24  
25 392 will also provide sufficient power to detect a clinically meaningful 20% between-group  
26  
27 393 difference in transition to frailty. For these calculations, we assumed an  $\alpha$  of 0.05, non-  
28  
29 394 compliance of 15% and a dropout rate of 15%.

### 30 31 32 33 395 **Statistical analysis**

34  
35 396 Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the  
36  
37 397 number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty  
38  
39 398 criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable.  
40  
41 399 The other study outcomes will be treated as continuous variables. The effect of group  
42  
43 400 allocation on continuously scored outcome measures at the four month and twelve month  
44  
45 401 follow-ups will be analysed using linear regression models with baseline scores entered into  
46  
47 402 the linear regression models as covariates. To aid interpretation of the change in frailty,  
48  
49 403 frailty will also be reported as a continuous variable. Statistical significance will be set at  
50  
51 404  $P < 0.05$  and we will report the differences in percentage or mean (95% confidence interval)  
52  
53 405 between the two groups at the 4-month and 12-month follow-ups.  
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58 406 We will test whether the response to the intervention is modified by the number of frailty  
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3 407 criteria present at baseline, by including an interaction term of study groups with number of  
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5 408 frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore  
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7 409 the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to  
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9 410 74% and  $\geq 75\%$ ) on the outcomes in the intervention group at 12-month follow-up. We will  
10  
11 411 examine baseline variables and if there are important between group differences we will  
12  
13 412 adjust for them in the models. The primary analyses will be conducted in accordance with the  
14  
15 413 intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in  
16  
17 414 the statistical analysis. The data monitoring committee, consisting of the Chief Investigator  
18  
19 415 and experienced researchers independent from the trial and funding, will analyse the  
20  
21 416 between-group difference in deaths every six months.  
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### 28 **Economic evaluation**

29  
30 419 The economic evaluation will be carried out and reported in accordance with health  
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32 420 economics reporting standards.[33] The economic evaluation will take the perspective of  
33  
34 421 Australian health and aged care service providers over a 12-month time period. Benefits will  
35  
36 422 be measured in terms of number of transitions to frailty prevented, mobility improvement and  
37  
38 423 QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness  
39  
40 424 analyses will include the cost of delivering the intervention and the cost of health and  
41  
42 425 community service utilisation. Bootstrap sampling will be used to examine the joint  
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44 426 probability distribution of costs and outcomes, with the creation of incremental cost-  
45  
46 427 effectiveness planes and cost-effectiveness acceptability curves for each outcome.  
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### 51 429 **Timeframe**

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53 430 Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in  
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55 431 October 2015.  
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3 433 **DISCUSSION**

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5 434 This trial will provide important information to guide intervention to improve outcomes for  
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7 435 older people who are pre-frail. Specifically, it will determine whether a multifactorial  
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10 436 interdisciplinary intervention reduces transition to frailty and deterioration in mobility among  
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12 437 pre-frail older men and women who live in the community. Frailty and the associated  
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14 438 negative effects such as disability, institutionalisation and hospitalisation are costly to  
15  
16 439 individuals, their families, the health system and society. Despite this cost, to our knowledge  
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18 440 there has been no research to date examining the effectiveness of intervention designed to  
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20  
21 441 reduce the transition to frailty among pre-frail older people.

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23 442

24  
25 443 The proposed multifactorial intervention will target the needs of each participant based upon  
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27 444 the characteristics of frailty present and comprehensive geriatric assessment. The exercise  
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29 445 component was designed using evidence from systematic reviews and randomised trials that  
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31 446 have demonstrated improved strength, balance and mobility in older people. We will  
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33 447 implement strategies to maximise adherence to the intervention, in line with research  
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35 448 suggesting good patient adherence increases the effectiveness of health interventions.[7,34]  
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37 449 The intervention is based on the program that was feasibly delivered to frail older people in  
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39 450 the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to  
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41 451 balance, strength and physical activity. Tailoring the exercises to the individual and ongoing  
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43 452 reassessment by the treating physiotherapist will ensure safety.

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49 454 Additional strengths of the study are the generalisability to pre-frail older people and aged  
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51 455 care health service settings, and the robust, but pragmatic, clinical trial design. This study  
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53 456 uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit  
54  
55 457 frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion  
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57 458 criteria. The intervention being examined is readily transferable to routine clinical practice in  
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3 459 the aged care health service setting and the interdisciplinary approach is relevant to several  
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5 460 professional groups in aged care.  
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7 461

8  
9 462 This study has some limitations. First, participants cannot be blinded to group allocation,  
10  
11 463 which is a potential source of bias due to possible differential reporting of the weight loss,  
12  
13 464 activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria,  
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15 465 and the co-primary outcome measure (CSPS) are performance-based, which should reduce  
16  
17 466 this bias. Second, as there is no frequency-matched social intervention for the control group,  
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19 467 we will not be able to exclude the impact of social aspects of the program on any difference  
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21 468 between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the  
22  
23 469 CHS phenotype is the most widely accepted instrument, other validated tools [36] and  
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25 470 attention to cognition could be considered in the clinical setting.  
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31 472 If this intervention is shown to be effective, there are major potential benefits to the older  
32  
33 473 population in terms of preventing transition to frailty and improving mobility. Avoiding  
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35 474 frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation  
36  
37 475 and institutionalisation, and the associated financial costs. Improved mobility may also result  
38  
39 476 in improved function and better quality of life for older people, their families and carers. If  
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41 477 cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of  
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43 478 health services. The findings will be disseminated through scientific and professional  
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45 479 conferences, and in peer-reviewed journals.  
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51 481 **List of abbreviations used**

52 482 CHS: Cardiovascular Health Study

53  
54 483 Pre-FIT: Pre-Frailty Intervention Trial

55  
56 484 WEBB: Weight Bearing Exercise for Better Balance  
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3 485 SPPB: Short Physical Performance Battery

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5 486 SD: standard deviation

6  
7 487 QALYs: Quality adjusted life years

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9 488 CSPS: lower extremity continuous summary performance score

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15  
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19  
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23  
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30 **497 Competing Interests**

31  
32 498 The authors declare that they have no competing interests.

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36 **500 Authors' contributions**

37  
38 501 NF drafted the manuscript. All authors are actively involved in the study. All authors read

39  
40 502 and approved the final manuscript.

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45 **504 References**

46  
47  
48 505 1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *Journal of the*

49  
50 506 *American Medical Directors Association* 2013;14(6):392-7.

51  
52 507 2. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward

53  
54 508 a better understanding of physiology and etiology: summary from the American Geriatrics

55  
56  
57  
58  
59  
60



- 1  
2  
3 509 Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am*  
4  
5 510 *Geriatr Soc* 2006;54(6):991-1001.  
6  
7 511 3. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J*  
8  
9 512 *Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56.  
10  
11 513 4. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and  
12  
13 514 comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*  
14  
15 515 2004;59(3):255-63.  
16  
17 516 5. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling  
18  
19 517 older persons: a systematic review. *Journal of the American Geriatrics Society*  
20  
21 518 2012;60(8):1487-92.  
22  
23 519 6. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for  
24  
25 520 the management of frailty: a systematic review. *J Aging Res* 2011;2011:569194.  
26  
27 521 7. Cameron ID, Fairhall N, Langron C, et al. A multifactorial interdisciplinary intervention  
28  
29 522 reduces frailty in older people: randomized trial. *BMC Med* 2013;11:65.  
30  
31 523 8. Gill TM, Gahbauer EA, Allore HG, et al. Transitions between frailty states among  
32  
33 524 community-living older persons. *Arch Intern Med* 2006;166(4):418-23.  
34  
35 525 9. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process.  
36  
37 526 *Gerontology* 2009;55(5):539-49.  
38  
39 527 10. Faber MJ, Bosscher RJ, Chin APMJ, et al. Effects of exercise programs on falls and  
40  
41 528 mobility in frail and pre-frail older adults: A multicenter randomized controlled trial. *Arch*  
42  
43 529 *Phys Med Rehabil* 2006;87(7):885-96.  
44  
45 530 11. Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in  
46  
47 531 physically frail, elderly persons who live at home. *N Engl J Med* 2002;347(14):1068-74.  
48  
49 532 12. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in  
50  
51 533 older people living in the community. *Cochrane Database Syst Rev* 2012(9):CD007146.  
52  
53 534 13. Daniel K. Wii-hab for pre-frail older adults. *Rehabil Nurs* 2012;37(4):195-201.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 535 14. Lustosa LP, Silva JP, Coelho FM, et al. Impact of resistance exercise program on  
4  
5 536 functional capacity and muscular strength of knee extensor in pre-frail community-dwelling  
6  
7 537 older women: a randomized crossover trial. *Rev Bras Fisioter* 2011;15(4):318-24.  
8  
9  
10 538 15. Coelho FM, Pereira DS, Lustosa LP, et al. Physical therapy intervention (PTI) increases  
11  
12 539 plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly  
13  
14 540 women. *Archives of gerontology and geriatrics* 2012;54(3):415-20.  
15  
16 541 16. Fairhall N, Aggar C, Kurrle SE, et al. Frailty Intervention Trial (FIT). *BMC Geriatrics*  
17  
18 542 2008;8:27.  
19  
20 543 17. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype.  
21  
22 544 *Journal of Gerontology* 2001;56A:M146-M56.  
23  
24 545 18. Holtzman J, Lurie N. Causes of increasing mortality in a nursing home population. *J Am*  
25  
26 546 *Geriatr Soc* 1996;44(3):258-64.  
27  
28 547 19. Beller EM, Gebiski V, Keech AC. Randomisation in clinical trials. *MJA*  
29  
30 548 2002;177(10):565-67.  
31  
32 549 20. Ko FC. The clinical care of frail, older adults. *Clin Geriatr Med* 2011;27(1):89-100.  
33  
34 550 21. Gallo JJ, Fulmer T, Paveza GJ, et al. *Handbook of Geriatric Assessment*. 3rd ed.  
35  
36 551 Maryland: Aspen Publishers, 2000.  
37  
38 552 22. Sherrington C. Exercise which challenges balance can prevent falls in older people: meta-  
39  
40 553 analysis of RCTs with meta-regression. *Australian Physiotherapy Association Conference*  
41  
42 554 *Week*. Cairns Australia, 2007.  
43  
44 555 23. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. "A practical method for  
45  
46 556 grading the cognitive state of patients for the clinician". *Journal of Psychiatric Research*  
47  
48 557 1975;12(3):189-98.  
49  
50 558 24. Onder G, Penninx BW, Lapuerta P, et al. Change in physical performance over time in  
51  
52 559 older women: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci*  
53  
54 560 2002;57(5):M289-93.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 561 25. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery  
4  
5 562 assessing lower extremity function: association with self-reported disability and prediction of  
6  
7 563 mortality and nursing home admission. *Journal of gerontology* 1994;49(2):M85-94.  
8  
9  
10 564 26. Hoyl MT, Alessi CA, Harker JO, et al. Development and testing of a five-item version of  
11  
12 565 the Geriatric Depression Scale. *J Am Geriatr Soc* 1999;47(7):873-8.  
13  
14 566 27. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Maryland State*  
15  
16 567 *Medical Journal* 1965;14:61-65.  
17  
18 568 28. Haley SM, Coster WJ, Andres PL, et al. Score comparability of short forms and  
19  
20 569 computerized adaptive testing: Simulation study with the activity measure for post-acute  
21  
22 570 care. *Arch Phys Med Rehabil* 2004;85(4):661-6.  
23  
24 571 29. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group.  
25  
26 572 *Annals of Medicine* 2001;33(5):337-43.  
27  
28 573 30. Latham NK, Anderson CS, Lee A, et al. A randomized, controlled trial of quadriceps  
29  
30 574 resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in  
31  
32 575 Elderly Subjects (FITNESS). *J Am Geriatr Soc* 2003;51(3):291-9.  
33  
34 576 31. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine-reporting of subgroup  
35  
36 577 analyses in clinical trials. *N Engl J Med* 2007;357(21):2189-94.  
37  
38 578 32. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials*  
39  
40 579 2000;21(3):167-89.  
41  
42 580 33. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation  
43  
44 581 Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health  
45  
46 582 Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value*  
47  
48 583 *Health* 2013;16(2):231-50.  
49  
50 584 34. DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment  
51  
52 585 outcomes: a meta-analysis. *Med Care* 2002;40(9):794-811.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 586 35. Abellan van Kan G, Rolland Y, Houles M, et al. The assessment of frailty in older adults.  
4  
5 587 *Clin Geriatr Med* 2010;26(2):275-86.  
6  
7 588 36. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty  
8  
9 589 in elderly people. *CMAJ* 2005;173(5):489-95.  
10  
11

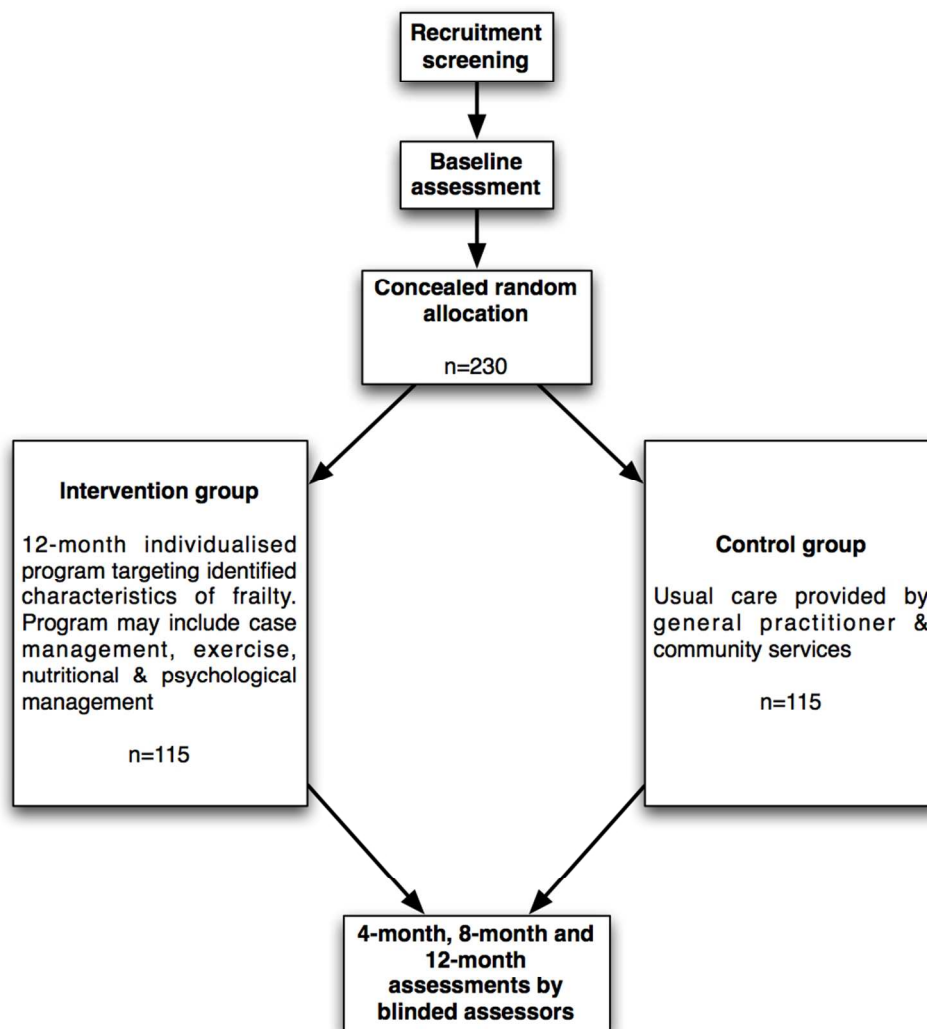
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16 591 **Figures**

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18 592 **Figure 1.** Overview of the flow of participants through the Pre-frailty Intervention Trial

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20 593 **Appendix 1.** Informed consent form

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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. Slow 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 a 12 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



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3 musculoskeletal symptom may develop as a result of the physical therapy  
4 intervention. This could be in the form of a muscular strain, or minor stress to  
5 ligaments or joint. In this unlikely event, the exercise program will be modified. There  
6 is also a slight risk of falling while exercising and this possibility will also be  
7 monitored.  
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### 10 11 12 13 **8. What happens if I suffer injury or complications as a result of the study?**

14 If you suffer any injuries or complications as a result of this study, you should  
15 contact the researcher visiting you as soon as possible, who will assist you in  
16 arranging appropriate medical treatment.  
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18 You may have a right to take legal action to obtain compensation for any injuries  
19 or complications resulting from the study. Compensation may be available if your  
20 injury or complication is caused by the project intervention or by the negligence of  
21 any of the research staff who visit you. If you receive compensation that includes  
22 an amount for medical expenses, you will be required to pay for your medical  
23 treatment from those compensation monies.  
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26 If you are not eligible for compensation for your injury or complication under the  
27 law, but are eligible for Medicare, then you can receive any medical treatment  
28 required for your injury or complication free of charge as a public patient in any  
29 Australian public hospital.  
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### 32 33 **9. Will I benefit from the study?**

34 This study aims to further develop medical knowledge and may improve future  
35 treatment of frailty; it may or may not be of direct benefit you.  
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### 38 39 **10. Will taking part in this study cost me anything, and will I be paid?**

40 Participation in this study will not cost you anything; neither will you be paid for  
41 your participation.  
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### 44 45 **11. How will my confidentiality be protected?**

46 Any identifiable information that is collected about you in connection with this study  
47 will remain confidential and will be disclosed only with your permission, or as  
48 required by law. Only the study researchers will have access to your details and  
49 results and all information will be held securely at Hornsby Ku-ring-gai Hospital.  
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### 52 53 **12. What happens with the results?**

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

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**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.**



Health  
Northern Sydney  
Local Health District

**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.

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

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12 I understand that should I have a complaint in regards to the conduct of this trial it may  
13 be directed to either Professor Ian Cameron on telephone (02) 9808-9236 or the  
14 Northern Sydney Coast Human Research Ethics Committee on (02) 9926 8106.  
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18 **Signature of subject** **Please PRINT name** **Date**  
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27 **Signature of Researcher** **Please PRINT name** **Date**  
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**Hornsby Ku-ring-gai Health Service**

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

**REVOCAION 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
<b>Administrative information</b>			
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
<b>Introduction</b>			
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

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**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:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	11
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those who	
7			enrol participants or assign interventions	
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9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	11
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions	
12			are assigned	
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14	Implementation	16c	Who will generate the allocation sequence, who will enrol	11
15			participants, and who will assign participants to interventions	
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18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	11
19	(masking)		participants, care providers, outcome assessors, data analysts),	
20			and how	
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22		17b	If blinded, circumstances under which unblinding is permissible,	11
23			and procedure for revealing a participant's allocated intervention	
24			during the trial	
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27	<b>Methods: Data collection, management, and analysis</b>			
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29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	16,17
30	methods		other trial data, including any related processes to promote data	
31			quality (eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
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36		18b	Plans to promote participant retention and complete follow-up,	17
37			including list of any outcome data to be collected for participants	
38			who discontinue or deviate from intervention protocols	
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41	Data	19	Plans for data entry, coding, security, and storage, including any	17
42	management		related processes to promote data quality (eg, double data entry;	
43			range checks for data values). Reference to where details of data	
44			management procedures can be found, if not in the protocol	
45				
46	Statistical	20a	Statistical methods for analysing primary and secondary	19,20
47	methods		outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
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50		20b	Methods for any additional analyses (eg, subgroup and adjusted	19,20
51			analyses)	
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53		20c	Definition of analysis population relating to protocol non-	20
54			adherence (eg, as randomised analysis), and any statistical	
55			methods to handle missing data (eg, multiple imputation)	
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**Methods: Monitoring**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	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**

25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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



1 2 3 4 5 6 7 8 9 10 11 12 13 14	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

15 16 17 18 19 20 21 22 23	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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

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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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.

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007091.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jan-2015
Complete List of Authors:	Fairhall, Nicola; The University of Sydney, Rehabilitation Studies Unit Kurrle, Susan; Hornsby Ku-ring-gai Health Service, Division of Rehabilitation and Aged Care Sherrington, Catherine; The George Institute for Global Health, Musculoskeletal Division Lord, Stephen; University of New South Wales, Neuroscience Research Australia Lockwood, Keri; The University of Sydney, Rehabilitation Studies Unit, Sydney Medical School John, Beatrice; The University of Sydney, Rehabilitation Studies Unit, Sydney Medical School Monaghan, Noeline; The University of Sydney, Rehabilitation Studies Unit, Sydney Medical School Howard, Kirsten; University of Sydney, School of Public Health Cameron, Ian; University of Sydney, Rehabilitation Studies Unit
<b>Primary Subject Heading</b>:	Geriatric medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	GERIATRIC MEDICINE, frail elderly, randomised trial

SCHOLARONE™  
Manuscripts

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3 1 **Effectiveness of a multifactorial intervention on preventing development of frailty in**  
4 2 **pre-frail older people. Study protocol for a randomised controlled trial.**  
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7 5 Nicola Fairhall<sup>1</sup>, Susan E Kurrle<sup>2</sup>, Catherine Sherrington<sup>3</sup>, Stephen R Lord<sup>4</sup>, Keri Lockwood<sup>2</sup>,  
8 6 Beatrice John<sup>2</sup>, Noeline Monaghan<sup>1</sup>, Kirsten Howard<sup>5</sup>, Ian D Cameron<sup>1, §</sup>  
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24 22

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46 44 IC: ian.cameron@sydney.edu.au  
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48 46  
49 47 **Key words:** frail elderly; randomized controlled trial; therapeutics; exercise.  
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51 49 **Word count:** 3913  
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3 50 **ABSTRACT**  
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52 **Introduction:** Frailty is a major concern due to its costly and widespread consequences, yet  
53 evidence of effective interventions to delay or reduce frailty is lacking. Our previous study  
54 found that a multifactorial intervention was feasible and effective in reducing frailty in older  
55 people who were already frail. Identifying and treating people in the pre-frail state may be an  
56 effective means to preventing or delaying frailty. This study describes a randomised  
57 controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on  
58 development of frailty in older people who are pre-frail.

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

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

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73 **Trial Registration:** Australian New Zealand Clinical Trials Registry:

74 ACTRN12613000043730.

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For peer review only

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3 76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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6 77     ▪ First randomised controlled trial to evaluate the effectiveness of an intervention on the  
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13 80     ▪ Randomised controlled trial with blinded assessors and intention-to-treat analysis.  
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17 82     ▪ Generalisable to community-dwelling pre-frail older people; there is an objective  
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19 83         measure of pre-frailty and minimal exclusion criteria. The intervention being  
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21 84         examined is readily transferable to routine clinical practice in the aged care health  
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23 85         service setting and the interdisciplinary approach is relevant to several professional  
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25 86         groups in aged care.  
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30 88     ▪ Lack of blinding of participants and staff delivering the intervention due to the nature  
31  
32 89         of the intervention.  
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3 91 **INTRODUCTION**  
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5

6 92 Intervention to prevent or delay frailty has important benefits for older people, health services  
7  
8 93 and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by  
9  
10 94 reduced strength, endurance and physiologic function, resulting in increased vulnerability to  
11  
12 95 functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between  
13  
14 96 non-frail and frail. Identifying and treating people in the pre-frail state may be an effective  
15  
16 97 way to prevent or delay frailty.  
17  
18  
19

20 98  
21 99 Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3]  
22  
23 100 which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and  
24  
25 101 slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People  
26  
27 102 are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria,  
28  
29 103 and frail if they meet three or more criteria. The frailty phenotype is predictive of falls,  
30  
31 104 disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have  
32  
33 105 significantly higher risk of developing these adverse outcomes than non-frail people, and frail  
34  
35 106 individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic  
36  
37 107 review found the prevalence of pre-frailty (as defined by the frailty phenotype) in  
38  
39 108 community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the  
40  
41 109 prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is  
42  
43 110 rising globally, the costs associated with frailty will increase in the future. Preventing or  
44  
45 111 delaying frailty has the potential to reduce the burden on individuals and society.  
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50 112  
51  
52 113 Research into interventions to prevent or reduce frailty is in its infancy. While studies have  
53  
54 114 found that outcomes for frail older people can be improved using multi-factorial interventions  
55  
56 115 such as comprehensive geriatric assessment, and single interventions including exercise  
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3 116 programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of  
4  
5 117 intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the  
6  
7 118 effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome  
8  
9  
10 119 (measured using the frailty phenotype), and found the intervention significantly reduced  
11  
12 120 frailty in frail community-dwelling older people.[7]  
13

14  
15  
16 122 Implementing interventions to pre-frail older people may prevent the development of frailty.  
17  
18 123 Older people transition between frailty states,[8] and pre-frail individuals have more than  
19  
20 124 twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to  
21  
22 125 frail is often endues from an acute medical event or a psychological stress exceeding the  
23  
24 126 person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the  
25  
26 127 impact of potential stressors may therefore reduce the risk of becoming frail. Evidence  
27  
28 128 suggests pre-frail older people may respond better to intervention than people who have  
29  
30 129 already moved to a frail state,[10,11] and because pre-frail people have significantly less  
31  
32 130 disability than frail people [3] there is potential for more intensive interventions.  
33  
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35

36 131  
37  
38 132 Few trials have identified and targeted pre-frail participants. Previous trials have included  
39  
40 133 samples that are probably pre-frail, for example people at risk of falling,[12] however studies  
41  
42 134 need to have pre-frailty as an inclusion criteria for results to be generalisable to this  
43  
44 135 population. Recent randomised trials [10,13,14] and an observational study [15] have  
45  
46 136 investigated the effects of exercise in people defined as pre-frail using the frailty phenotype;  
47  
48 137 exercise appears to improve function in pre-frail people, however larger studies are needed.  
49  
50 138 To our knowledge, no intervention has been developed to specifically prevent the transition  
51  
52 139 to frailty in pre-frail older people.  
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3 141 We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial  
4  
5 142 that aims to determine whether delivering a multifactorial, interdisciplinary intervention to  
6  
7 143 older people who are pre-frail prevents progression to frailty and improves mobility. We will  
8  
9 144 implement a modification of the intervention previously found to reduce frailty and improve  
10  
11 145 mobility in frail older people [16] to determine whether pre-frail participants receive similar  
12  
13 146 benefits with respect to frailty levels and mobility. To our knowledge this will be the first  
14  
15 147 study to examine the effects of an intervention specifically targeting degree of frailty among  
16  
17 148 older people who are pre-frail. The primary research question is: Does the multifactorial  
18  
19 149 interdisciplinary intervention prevent the progression to frailty (assessed with a frailty  
20  
21 150 phenotype score) and improve mobility among pre-frail older people, when compared with  
22  
23 151 usual care?  
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## 30 **METHODS AND DESIGN**

### 31 **Design**

32  
33  
34 155 A randomised controlled trial will be conducted among 230 participants who are pre-frail.  
35  
36 156 Figure 1 gives an overview of the study design. The Northern Sydney Local Health District  
37  
38 157 Health Research Ethics Committee approved this study (Research Protocol Number 1207-  
39  
40 158 213M) and all participants will give written informed consent prior to randomisation  
41  
42 159 (Appendix 1). The study is registered with the Australia New Zealand Clinical Trials Register  
43  
44 160 ACTRN12613000043730.  
45  
46  
47  
48

### 49 **Participants**

50  
51  
52 163 Potential participants will be identified by clinicians working in hospital and community  
53  
54 164 sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-  
55  
56 165 ring-gai Health Service, in Sydney, Australia.  
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60

1  
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3 167 Participants who fulfill the following inclusion criteria will be invited to participate:  
4

- 5 168 1. Male or female, aged 70 years or older  
6  
7 169 2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)  
8  
9 170 3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score >  
10  
11 23);  
12  
13

14 172 People will be ineligible to participate in the trial if they:

- 15  
16 173 1. Live in a residential aged care facility  
17  
18 174 2. Have an estimated life expectancy of less than 12 months (estimated by a score of  $\leq 3$   
19  
20 on a modified version of the Implicit Illness Severity Scale [18])  
21  
22 175  
23 176 3. Currently receive a treatment program from a rehabilitation facility  
24  
25  
26 177

27  
28 178 Table 1.

Characteristic	Criteria
Weight loss/ Shrinking	Self-report of $\geq 4.5$ kg lost unintentionally in previous 12 months or loss of $\geq 5\%$ 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.
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179

**180 Randomisation**

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

187

**188 Allocation concealment**

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

195

**196 Intervention**

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

1  
2  
3 200 medical management of health conditions, allied health input, assessment of care needs and  
4  
5 201 provision of care.  
6

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8 202

9  
10 203 Participants in the intervention group will receive an interdisciplinary, multifactorial  
11  
12 204 intervention for one year. The intervention will be individually tailored to each participant  
13  
14 205 based on the following: a) the CHS frailty characteristics present at baseline assessment; b)  
15  
16 206 additional problems identified during a detailed assessment by the physiotherapist providing  
17  
18 207 the intervention program, plus other relevant members of the interdisciplinary team; c)  
19  
20 208 ongoing reassessment by the interdisciplinary team throughout the intervention period. The  
21  
22 209 assessment and intervention will be underpinned by the principles of geriatric evaluation and  
23  
24 210 management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician,  
25  
26 211 a rehabilitation physician, a dietician and a nurse will deliver the intervention. All  
27  
28 212 intervention staff will have experience in delivering interventions to older people. Case  
29  
30 213 management and regular case conferences will assist coordination of the interdisciplinary  
31  
32 214 delivery of the intervention. The treating physiotherapist will have the case coordinator role,  
33  
34 215 liaising with the participant, family, health professionals and service providers, plus  
35  
36 216 coordinating services as indicated.  
37  
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39

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41 217

42  
43 218 The intervention will be delivered primarily in participants' homes, with additional  
44  
45 219 community exercise programs and outpatient appointments (for example, podiatrist, memory  
46  
47 220 clinic, continence clinic) offered when indicated.  
48

49  
50 221

51  
52 222 The interventions targeting the CHS frailty characteristics are described below.  
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3 224 *Weight loss*

4  
5 225 A dietician will evaluate nutritional intake if the participant is not already effectively  
6  
7 226 addressing their recent weight loss. If the participant's body mass index is <18.5 or mid  
8  
9 227 upper arm circumference is < the 10<sup>th</sup> percentile (using Australian gender and age specific  
10  
11 228 norms), nutritional supplementation will be offered using commercially available, high  
12  
13 229 protein, high energy, supplements. Home delivered meals will be recommended if  
14  
15 230 appropriate clinical criteria apply.  
16  
17  
18  
19

20  
21

22 232 *Exhaustion*

23 233 Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale  
24  
25 234 score is high. Where the participant is socially isolated, opportunities to encourage greater  
26  
27 235 social engagement will be identified, e.g. day activity groups, physical activity programs in  
28  
29 236 the community, and telephone contact with volunteers.  
30  
31

32 237

33  
34 238 *Grip weakness, slow four metre walk time, or low physical activity level*

35  
36 239 A physiotherapist experienced in aged care will visit the participant's home ten times in the  
37  
38 240 12 months study period. There will be five sessions in the first three months after  
39  
40 241 randomisation, and five sessions over the following nine months. Visits will be 60 to 120  
41  
42 242 minutes duration. The physiotherapist will prescribe a home exercise program to be  
43  
44 243 performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree  
45  
46 244 of difficulty and number of repetitions prescribed will be based upon assessment of the  
47  
48 245 individual participant's abilities. Lower limb balance and strengthening exercises will utilise  
49  
50 246 the Weight Bearing Exercise for Better Balance (WEBB) program, available at  
51  
52 247 [www.webb.org.au](http://www.webb.org.au).<sup>[22]</sup> The program targets strength and control of the lower limb extensor  
53  
54 248 muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up  
55  
56 249 from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a  
57  
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1  
2  
3 250 wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as  
4  
5 251 appropriate. Balance will be targeted with exercises performed in standing with a  
6  
7 252 progressively narrowed base (feet together, tandem stance, single leg stance), stepping,  
8  
9  
10 253 walking and reaching. Upper limb support will be minimised in order to adequately challenge  
11  
12 254 balance, but to ensure safety the environment will be set up with stable supports (e.g. bench  
13  
14 255 or table) close by that can be held as necessary. In addition, if upper limb weakness is  
15  
16 256 creating functional problems, then the physiotherapist may prescribe upper limb exercises  
17  
18 257 incorporating theraband or free weights for resistance. The physiotherapist will regularly  
19  
20  
21 258 review and modify the optimal intensity and type of exercises for each participant to ensure  
22  
23 259 the intervention remains appropriate and challenging over the study period. We will  
24  
25 260 encourage family members or carers to assist with the exercise program when this is  
26  
27 261 indicated.  
28

29  
30 262  
31  
32 263 Appropriate safe mobility programs will be prescribed if participants have low activity levels,  
33  
34 264 reduced endurance or specific functional goals. Feedback will be provided via monitoring of  
35  
36 265 distance/time or via a pedometer or *FitBit* (internet-linked pedometer). Participants will be  
37  
38 266 encouraged and supported in increasing their physical activity using exercise equipment that  
39  
40 267 they have at home, as well as community physical activity programs (such as Tai Chi or  
41  
42 268 strength and balance classes), community exercise facilities (such as gymnasiums and  
43  
44 269 swimming pools) and a return to past leisure activities such as golf and bowls.  
45  
46

47 270  
48  
49 271 In addition to the interventions targeting the CHS frailty characteristics, individually-tailored  
50  
51 272 intervention will address additional problems identified during assessment. Intervention may  
52  
53 273 include, but will not be limited to, the following examples.  
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- 1  
2  
3 275 • General health status will be assessed and intervention tailored to each individual's  
4  
5 276 problems. Where indicated, chronic disease management programs will be implemented  
6  
7 277 or reinforced in conjunction with existing health services. We will use the principles of  
8  
9  
10 278 comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and  
11  
12 279 conditions such as incontinence, osteoporosis and impaired cognition. The rehabilitation  
13  
14 280 physician and geriatrician will play a central role in assessment and recommendations for  
15  
16 281 ongoing intervention.  
17  
18  
19 282 • The rehabilitation physician or geriatrician will review medications used and will discuss  
20  
21 283 any questionable medication use with the participant's general practitioner. Poor  
22  
23 284 compliance with medications will be addressed by initiation or reinforcement of strategies  
24  
25 285 such as education about medications, medication packaging in blister packs and reminder  
26  
27 286 cards.  
28  
29  
30 287 • Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia,  
31  
32 288 and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and  
33  
34 289 Parkinson's Disease exercise classes.  
35  
36 290 • The team will refer to agencies that provide assessments and provision of care and  
37  
38 291 services. Examples are the Aged Care Assessment Team for assessment for packages of  
39  
40 292 care, community nursing and service providers.  
41  
42  
43 293 • If transport is required, we will arrange referral to community transport services, taxi  
44  
45 294 subsidy schemes and mobility parking schemes as appropriate.  
46  
47 295 • Reduced social interaction will be targeted by facilitating attendance at community-based  
48  
49 296 groups, day centres, clubs and exercise groups, as well as by arranging telephone contact  
50  
51 297 with a volunteer.  
52  
53  
54 298 • We will advise on meal delivery services and frozen meals if this assistance is needed.  
55  
56 299 • Mobility aids and other equipment will be recommended, obtained and set up where  
57  
58 300 indicated. This may involve referral to an occupational therapist for environmental  
59  
60



1  
2  
3 301 modifications.

4  
5 302 • Advice on appropriate footwear will be provided if shoes are suboptimal.

6  
7 303 • Ergonomic alterations will be made to optimise home office safety.

8  
9 304 • If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls  
10 and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program)

11 305 available in the study area, in addition to the WEBB exercise program. Safety concerns

12 306 will also be addressed with information about falls prevention, personal alarms and hip

13 307 protectors.

14 308  
15 309 • If the participant cares for another person or the participant has a carer who needs help,

16 310 the carer's needs will be assessed and contact with Carers Australia will be suggested.

17 311

18 312 The physiotherapist and participant will collaborate to set measurable goals within three

19 313 months of recruitment. The goals will be based upon the CHS frailty characteristics present

20 314 (such as goals relating to diet, functional consequences of weakness or amount of physical

21 315 activity), or problems identified during geriatric assessment (such as establishing formal links

22 316 with a diabetes educator, understanding medications or obtaining a care package). The goals

23 317 will be documented, reviewed each session by the physiotherapist and participant, and new

24 318 goals will be set when new issues are targeted.

25 319

26 320 The physiotherapist will promote adherence to the intervention using strategies including

27 321 goal setting, a flexible time-frame for intervention delivery, recording of exercise completion,

28 322 and involvement of family and carers. In addition, programs will be tailored to suit individual

29 323 requirements and interventions will be designed to be varied, sustainable and enjoyable.

30 324

31 325 **Data collection**

32 326 Participants will undergo three home-based assessments. The baseline measures will be

1  
2  
3 327 assessed prior to randomisation and further assessments will be conducted four and 12  
4  
5 328 months after randomisation. Additional health service utilisation data will be collected via a  
6  
7 329 telephone call at eight months. Blinded assessors (experienced health professionals) will  
8  
9  
10 330 conduct follow-up assessments. To ensure blinding, participants will be instructed not to  
11  
12 331 disclose group allocation to the assessors. The assessors' perception of group allocation will  
13  
14 332 be assessed, to evaluate the success of assessor blinding.

15  
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17 333

18 334 **Outcome measures**

19  
20 335 Demographic and health information will be collected at baseline. Cognitive function will be  
21  
22 336 assessed with the Mini Mental State Examination.[23]

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24  
25 337

26  
27 338 - *Primary outcomes*

28  
29 339 The primary outcomes measured are frailty and mobility, measured at four and 12 months.

30  
31 340 Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty  
32  
33 341 phenotype evaluates five components of the frailty syndrome and allocates one point for each  
34  
35 342 criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are  
36  
37 343 defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using  
38  
39 344 the lower extremity continuous summary performance score (CSPS),[24] with data collected  
40  
41 345 using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability  
42  
43 346 to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem  
44  
45 347 positions, time taken to walk four metres, and time to rise from a chair and return to the  
46  
47 348 seated position five times.

48  
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50 349

51  
52 350 - *Secondary outcomes*

53  
54 351 1. Psychological status will be assessed using the five-item version of the Geriatric  
55  
56 352 Depression Scale.[26]

- 1  
2  
3 353 2. Activities of daily living will be measured using the Barthel Index [27] (100 point  
4 version). The mobility component of the Activity Measure for Post Acute Care [28] will  
5 354  
6 measure self reported activity level using Item Response Theory and computer-adaptive  
7 355  
8 testing.  
9 356  
10  
11 357 3. Gait speed will be measured using the four-metre walk test.  
12  
13 358 4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility  
14 weights to allow calculation of Quality adjusted life years (QALYs) for use in the  
15 359  
16 economic evaluation.[29]  
17 360  
18  
19 361 5. Falls, hospitalisations and admissions to residential aged care facilities will be collected  
20 via telephone at four, eight and 12 months and will also be used in the economic analyses.  
21 362  
22  
23 363 6. Health and community service use will be recorded at four, eight and 12 months and will  
24 be used in economic analyses.  
25 364  
26  
27  
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30 365

31 366 - *Additional measures*

32  
33  
34 367 Adherence measurements will record the acceptance of health and other services by the study  
35 participant. The treating physiotherapist will estimate a global level of adherence (in five  
36 368  
37 categories: 0%, <25%, 25-49%, 50-74% and  $\geq 75\%$ ) during the 12-month intervention. The  
38 369  
39 treating physiotherapist will evaluate goal attainment in the intervention group using a four-  
40 370  
41 point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal  
42 371  
43 exceeded.  
44 372  
45  
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47 373

48  
49 374 Adverse events will be defined as medical events or injuries arising as a consequence of the  
50 trial and resulting in medical attention or restricted activities of daily living for more than two  
51 375  
52 days.[30] Deaths will be documented.  
53 376  
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56 377

57  
58 378 **Sample size calculation**  
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3 379 An *a priori* power analysis determined 230 participants will need to be recruited, to provide  
4  
5 380 80% power to detect a clinically and statistically significant 15% between group difference in  
6  
7 381 lower extremity continuous summary performance score (SD = 0.7).[25] This sample size  
8  
9 382 will also provide sufficient power to detect a clinically meaningful 20% between-group  
10  
11 383 difference in transition to frailty. For these calculations, we assumed an  $\alpha$  of 0.05, non-  
12  
13 384 compliance of 15% and a dropout rate of 15%.

### 17 385 **Statistical analysis**

18  
19 386 Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the  
20  
21 387 number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty  
22  
23 388 criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable.  
24  
25 389 The other study outcomes will be treated as continuous variables. The effect of group  
26  
27 390 allocation on continuously scored outcome measures at the four month and twelve month  
28  
29 391 follow-ups will be analysed using linear regression models with baseline scores entered into  
30  
31 392 the linear regression models as covariates. To aid interpretation of the change in frailty,  
32  
33 393 frailty will also be reported as a continuous variable. Statistical significance will be set at  
34  
35 394  $P < 0.05$  and we will report the differences in percentage or mean (95% confidence interval)  
36  
37 395 between the two groups at the 4-month and 12-month follow-ups.

38  
39 396 We will test whether the response to the intervention is modified by the number of frailty  
40  
41 397 criteria present at baseline, by including an interaction term of study groups with number of  
42  
43 398 frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore  
44  
45 399 the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to  
46  
47 400 74% and  $\geq 75\%$ ) on the outcomes in the intervention group at 12-month follow-up. We will  
48  
49 401 examine baseline variables and if there are important between group differences we will  
50  
51 402 adjust for them in the models. The primary analyses will be conducted in accordance with the  
52  
53 403 intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in  
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1  
2  
3 404 the statistical analysis.  
4

5 405 Participants will be provided with their own results on request. The overall results will be  
6  
7 406 available to participants once the final results are published. It is anticipated that participants  
8  
9 407 will register their interest in receiving this information when their participation in the study  
10  
11 408 ends.  
12

### 13 14 15 409 **Economic evaluation**

16  
17 410 The economic evaluation will be carried out and reported in accordance with health  
18  
19 411 economics reporting standards.[33] The economic evaluation will take the perspective of  
20  
21 412 Australian health and aged care service providers over a 12-month time period. Benefits will  
22  
23 413 be measured in terms of number of transitions to frailty prevented, mobility improvement and  
24  
25 414 QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness  
26  
27 415 analyses will include the cost of delivering the intervention and the cost of health and  
28  
29 416 community service utilisation. Bootstrap sampling will be used to examine the joint  
30  
31 417 probability distribution of costs and outcomes, with the creation of incremental cost-  
32  
33 418 effectiveness planes and cost-effectiveness acceptability curves for each outcome.  
34  
35

36  
37 419

### 38 39 420 **Timeframe**

40  
41 421 Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in  
42  
43 422 October 2015.  
44

45  
46 423

### 47 48 424 **DISCUSSION**

49  
50 425 This trial will provide important information to guide intervention to improve outcomes for  
51  
52 426 older people who are pre-frail. Specifically, it will determine whether a multifactorial  
53  
54 427 interdisciplinary intervention reduces transition to frailty and deterioration in mobility among  
55  
56 428 pre-frail older men and women who live in the community. Frailty and the associated  
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3 429 negative effects such as disability, institutionalisation and hospitalisation are costly to  
4  
5 430 individuals, their families, the health system and society. Despite this cost, to our knowledge  
6  
7 431 there has been no research to date examining the effectiveness of intervention designed to  
8  
9  
10 432 reduce the transition to frailty among pre-frail older people.

433

14 434 The proposed multifactorial intervention will target the needs of each participant based upon  
15  
16 435 the characteristics of frailty present and comprehensive geriatric assessment. The exercise  
17  
18 436 component was designed using evidence from systematic reviews and randomised trials that  
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21 437 have demonstrated improved strength, balance and mobility in older people. We will  
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23 438 implement strategies to maximise adherence to the intervention, in line with research  
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25 439 suggesting good patient adherence increases the effectiveness of health interventions.[7,34]

27 440 The intervention is based on the program that was feasibly delivered to frail older people in  
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29 441 the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to  
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31 442 balance, strength and physical activity. Tailoring the exercises to the individual and ongoing  
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33 443 reassessment by the treating physiotherapist will ensure safety.

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38 445 Additional strengths of the study are the generalisability to pre-frail older people and aged  
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40 446 care health service settings, and the robust, but pragmatic, clinical trial design. This study  
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42 447 uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit  
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44 448 frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion  
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46 449 criteria. The intervention being examined is readily transferable to routine clinical practice in  
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48 450 the aged care health service setting and the interdisciplinary approach is relevant to several  
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50 451 professional groups in aged care.

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56 453 This study has some limitations. First, participants cannot be blinded to group allocation,  
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58 454 which is a potential source of bias due to possible differential reporting of the weight loss,  
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3 455 activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria,  
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5 456 and the co-primary outcome measure (CSPS) are performance-based, which should reduce  
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7 457 this bias. Second, as there is no frequency-matched social intervention for the control group,  
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9 458 we will not be able to exclude the impact of social aspects of the program on any difference  
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11 459 between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the  
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13 460 CHS phenotype is the most widely accepted instrument, other validated tools [36] and  
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15 461 attention to cognition could be considered in the clinical setting.  
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21 463 If this intervention is shown to be effective, there are major potential benefits to the older  
22  
23 464 population in terms of preventing transition to frailty and improving mobility. Avoiding  
24  
25 465 frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation  
26  
27 466 and institutionalisation, and the associated financial costs. Improved mobility may also result  
28  
29 467 in improved function and better quality of life for older people, their families and carers. If  
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31 468 cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of  
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33 469 health services. The findings will be disseminated through scientific and professional  
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35 470 conferences, and in peer-reviewed journals.  
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#### 40 472 **List of abbreviations used**

41  
42  
43 473 CHS: Cardiovascular Health Study  
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45 474 Pre-FIT: Pre-Frailty Intervention Trial  
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47 475 WEBB: Weight Bearing Exercise for Better Balance  
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49 476 SPPB: Short Physical Performance Battery  
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51 477 SD: standard deviation  
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53 478 QALYs: Quality adjusted life years  
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55 479 CSPS: lower extremity continuous summary performance score  
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3 481 **Acknowledgements and funding**  
4

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6  
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8  
9  
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11  
12 485 Research Council Practitioner Fellowship.  
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14 486  
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16 487 **Competing Interests**  
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18 488 The authors declare that they have no competing interests.  
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23 490 **Authors' contributions**  
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25 491 NF drafted the manuscript. CS, SL, SK and IC are chief investigators on the study. NF, KL,  
26  
27 492 NM, BJ and KH are actively involved in the study. All authors read and approved the final  
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29 493 manuscript.  
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34 495 **References**  
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- 36  
37 496 1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *Journal of the*  
38  
39 497 *American Medical Directors Association* 2013;14(6):392-7.  
40  
41 498 2. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward  
42  
43 499 a better understanding of physiology and etiology: summary from the American Geriatrics  
44  
45 500 Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am*  
46  
47 501 *Geriatr Soc* 2006;54(6):991-1001.  
48  
49 502 3. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J*  
50  
51 503 *Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56.  
52  
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2  
3 504 4. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and  
4  
5 505 comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*  
6  
7 506 2004;59(3):255-63.  
8  
9  
10 507 5. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling  
11  
12 508 older persons: a systematic review. *Journal of the American Geriatrics Society*  
13  
14 509 2012;60(8):1487-92.  
15  
16 510 6. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for  
17  
18 511 the management of frailty: a systematic review. *J Aging Res* 2011;2011:569194.  
19  
20  
21 512 7. Cameron ID, Fairhall N, Langron C, et al. A multifactorial interdisciplinary intervention  
22  
23 513 reduces frailty in older people: randomized trial. *BMC Med* 2013;11:65.  
24  
25 514 8. Gill TM, Gahbauer EA, Allore HG, et al. Transitions between frailty states among  
26  
27 515 community-living older persons. *Arch Intern Med* 2006;166(4):418-23.  
28  
29  
30 516 9. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process.  
31  
32 517 *Gerontology* 2009;55(5):539-49.  
33  
34 518 10. Faber MJ, Bosscher RJ, Chin APMJ, et al. Effects of exercise programs on falls and  
35  
36 519 mobility in frail and pre-frail older adults: A multicenter randomized controlled trial. *Arch*  
37  
38 520 *Phys Med Rehabil* 2006;87(7):885-96.  
39  
40  
41 521 11. Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in  
42  
43 522 physically frail, elderly persons who live at home. *N Engl J Med* 2002;347(14):1068-74.  
44  
45 523 12. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in  
46  
47 524 older people living in the community. *Cochrane Database Syst Rev* 2012(9):CD007146.  
48  
49  
50 525 13. Daniel K. Wii-hab for pre-frail older adults. *Rehabil Nurs* 2012;37(4):195-201.  
51  
52 526 14. Lustosa LP, Silva JP, Coelho FM, et al. Impact of resistance exercise program on  
53  
54 527 functional capacity and muscular strength of knee extensor in pre-frail community-dwelling  
55  
56 528 older women: a randomized crossover trial. *Rev Bras Fisioter* 2011;15(4):318-24.  
57  
58  
59  
60

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2  
3 529 15. Coelho FM, Pereira DS, Lustosa LP, et al. Physical therapy intervention (PTI) increases  
4  
5 530 plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly  
6  
7 531 women. *Archives of gerontology and geriatrics* 2012;54(3):415-20.  
8  
9  
10 532 16. Fairhall N, Aggar C, Kurrle SE, et al. Frailty Intervention Trial (FIT). *BMC Geriatrics*  
11  
12 533 2008;8:27.  
13  
14 534 17. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype.  
15  
16 535 *Journal of Gerontology* 2001;56A:M146-M56.  
17  
18 536 18. Holtzman J, Lurie N. Causes of increasing mortality in a nursing home population. *J Am*  
19  
20 537 *Geriatr Soc* 1996;44(3):258-64.  
21  
22  
23 538 19. Beller EM, Gebiski V, Keech AC. Randomisation in clinical trials. *MJA*  
24  
25 539 2002;177(10):565-67.  
26  
27 540 20. Ko FC. The clinical care of frail, older adults. *Clin Geriatr Med* 2011;27(1):89-100.  
28  
29 541 21. Gallo JJ, Fulmer T, Paveza GJ, et al. *Handbook of Geriatric Assessment*. 3rd ed.  
30  
31 542 Maryland: Aspen Publishers, 2000.  
32  
33  
34 543 22. Sherrington C. Exercise which challenges balance can prevent falls in older people: meta-  
35  
36 544 analysis of RCTs with meta-regression. *Australian Physiotherapy Association Conference*  
37  
38 545 *Week*. Cairns Australia, 2007.  
39  
40  
41 546 23. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. "A practical method for  
42  
43 547 grading the cognitive state of patients for the clinician". *Journal of Psychiatric Research*  
44  
45 548 1975;12(3):189-98.  
46  
47  
48 549 24. Onder G, Penninx BW, Lapuerta P, et al. Change in physical performance over time in  
49  
50 550 older women: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci*  
51  
52 551 2002;57(5):M289-93.  
53  
54 552 25. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery  
55  
56 553 assessing lower extremity function: association with self-reported disability and prediction of  
57  
58 554 mortality and nursing home admission. *Journal of gerontology* 1994;49(2):M85-94.  
59  
60

- 1  
2  
3 555 26. Hoyl MT, Alessi CA, Harker JO, et al. Development and testing of a five-item version of  
4  
5 556 the Geriatric Depression Scale. *J Am Geriatr Soc* 1999;47(7):873-8.  
6  
7 557 27. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Maryland State*  
8  
9 558 *Medical Journal* 1965;14:61-65.  
10  
11 559 28. Haley SM, Coster WJ, Andres PL, et al. Score comparability of short forms and  
12  
13 560 computerized adaptive testing: Simulation study with the activity measure for post-acute  
14  
15 561 care. *Arch Phys Med Rehabil* 2004;85(4):661-6.  
16  
17 562 29. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group.  
18  
19 563 *Annals of Medicine* 2001;33(5):337-43.  
20  
21 564 30. Latham NK, Anderson CS, Lee A, et al. A randomized, controlled trial of quadriceps  
22  
23 565 resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in  
24  
25 566 Elderly Subjects (FITNESS). *J Am Geriatr Soc* 2003;51(3):291-9.  
26  
27 567 31. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine-reporting of subgroup  
28  
29 568 analyses in clinical trials. *N Engl J Med* 2007;357(21):2189-94.  
30  
31 569 32. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials*  
32  
33 570 2000;21(3):167-89.  
34  
35 571 33. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation  
36  
37 572 Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health  
38  
39 573 Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value*  
40  
41 574 *Health* 2013;16(2):231-50.  
42  
43 575 34. DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment  
44  
45 576 outcomes: a meta-analysis. *Med Care* 2002;40(9):794-811.  
46  
47 577 35. Abellan van Kan G, Rolland Y, Houles M, et al. The assessment of frailty in older adults.  
48  
49 578 *Clin Geriatr Med* 2010;26(2):275-86.  
50  
51 579 36. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty  
52  
53 580 in elderly people. *CMAJ* 2005;173(5):489-95.  
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582 **Figures**

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

584 **Appendix 1.** Informed consent form

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7 **1 Effectiveness of a multifactorial intervention on preventing development of frailty in**  
8 **2 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:** 3913857

50 **ABSTRACT**

51  
52 **Introduction:** Frailty is a major concern due to its costly and widespread consequences, yet  
53 evidence of effective interventions to delay or reduce frailty is lacking. Our previous study  
54 found that a multifactorial intervention was feasible and effective in reducing frailty in older  
55 people who were already frail. Identifying and treating people in the pre-frail state may be an  
56 effective means to preventing or delaying frailty. This study describes a randomised  
57 controlled trial that aims to evaluate the effectiveness of a multifactorial intervention on  
58 development of frailty in older people who are pre-frail.

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

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

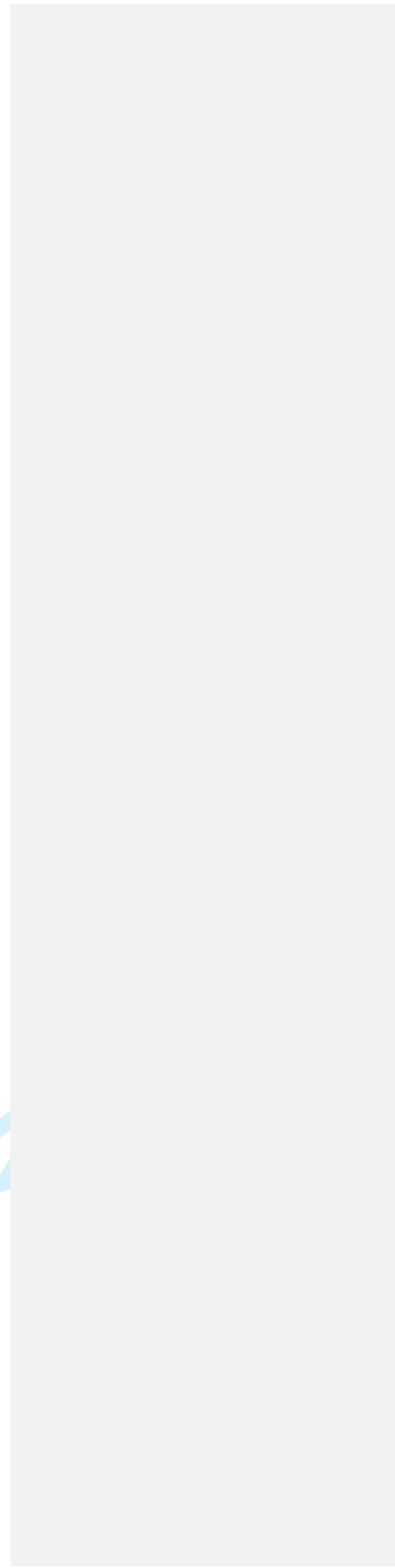
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73 **Trial Registration:** Australian New Zealand Clinical Trials Registry:

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76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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10 77     ▪ First randomised controlled trial to evaluate the effectiveness of an intervention on the  
11 78         development of frailty in older people who are pre-frail.  
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13 79  
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15 80     ▪ ~~R~~Single-centre randomised controlled trial with blinded assessors and intention-to-  
16 81         treat analysis.  
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18 82  
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20 83     ▪ Generalisable to community-dwelling pre-frail older people; there is an objective  
21 84         measure of pre-frailty and minimal exclusion criteria. The intervention being  
22 85         examined is readily transferable to routine clinical practice in the aged care health  
23 86         service setting and the interdisciplinary approach is relevant to several professional  
24 87         groups in aged care.  
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26 88  
27 89     ▪ Lack of blinding of participants and staff delivering the intervention due to the nature  
28 90         of the intervention.  
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7 92 **INTRODUCTION**  
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9 93 Intervention to prevent or delay frailty has important benefits for older people, health services  
10 94 and society.[1,2] Frailty is a medical syndrome with numerous causes, characterised by  
11 95 reduced strength, endurance and physiologic function, resulting in increased vulnerability to  
12 96 functional decline, dependence and/or death.[1] Pre-frailty is an intermediate stage between  
13 97 non-frail and frail. Identifying and treating people in the pre-frail state may be an effective  
14 98 way to prevent or delay frailty.  
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22 99  
23 100 Frailty can be defined using the Cardiovascular Health Study (CHS) frailty phenotype [3]  
24 101 which contains five criteria (unexplained weight loss, weakness, low activity, exhaustion and  
25 102 slowness) that reflect underlying dysregulation in multiple physiologic processes.[4] People  
26 103 are classified as non-frail if they meet no criteria, pre-frail if they meet one or two criteria,  
27 104 and frail if they meet three or more criteria. The frailty phenotype is predictive of falls,  
28 105 disability, institutionalisation, hospitalisation and mortality; pre-frail individuals have  
29 106 significantly higher risk of developing these adverse outcomes than non-frail people, and frail  
30 107 individuals have higher risk still.[3] Pre-frailty and frailty are common; a recent systematic  
31 108 review found the prevalence of pre-frailty (as defined by the frailty phenotype) in  
32 109 community-dwelling people aged 65 years or older, was 38% to 53% (mean 44.2%), and the  
33 110 prevalence of frailty was 4% to 17% (mean 9.9%).[5] As the proportion of older people is  
34 111 rising globally, the costs associated with frailty will increase in the future. Preventing or  
35 112 delaying frailty has the potential to reduce the burden on individuals and society.  
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50 114 Research into interventions to prevent or reduce frailty is in its infancy. While studies have  
51 115 found that outcomes for frail older people can be improved using multi-factorial interventions  
52 116 such as comprehensive geriatric assessment, and single interventions including exercise  
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7 117 programs,[6] nutritional supplementation and reduction of polypharmacy,[1] the effect of  
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9 118 intervention on frailty itself is seldom examined. Our recent randomised trial evaluated the  
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11 119 effect of a multifactorial interdisciplinary intervention on frailty as a primary outcome  
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13 120 (measured using the frailty phenotype), and found the intervention significantly reduced  
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15 121 frailty in frail community-dwelling older people.[7]  
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122

18 123 Implementing interventions to pre-frail older people may prevent the development of frailty.

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20 124 Older people transition between frailty states,[8] and pre-frail individuals have more than  
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22 125 twice the risk of becoming frail compared to non-frail people.[3] Transition from pre-frail to  
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24 126 frail is often endues from an acute medical event or a psychological stress exceeding the  
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26 127 person's capacity for recovery.[9] Intervention to increase reserve capacity and reduce the  
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28 128 impact of potential stressors may therefore reduce the risk of becoming frail. Evidence  
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30 129 suggests pre-frail older people may respond better to intervention than people who have  
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32 130 already moved to a frail state,[10,11] and because pre-frail people have significantly less  
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34 131 disability than frail people [3] there is potential for more intensive interventions.  
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37 133 Few trials have identified and targeted pre-frail participants. Previous trials have included  
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39 134 samples that are probably pre-frail, for example people at risk of falling,[12] however studies  
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41 135 need to have pre-frailty as an inclusion criteria for results to be generalisable to this  
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43 136 population. Recent randomised trials [10,13,14] and an observational study [15] have  
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45 137 investigated the effects of exercise in people defined as pre-frail using the frailty phenotype;  
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47 138 exercise appears to improve function in pre-frail people, however larger studies are needed.  
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49 139 To our knowledge, no intervention has been developed to specifically prevent the transition  
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51 140 to frailty in pre-frail older people.

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7 142 We plan to conduct the Pre-Frailty Intervention Trial (Pre-FIT); a randomised controlled trial  
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9 143 that aims to determine whether delivering a multifactorial, interdisciplinary intervention to  
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11 144 older people who are pre-frail prevents progression to frailty and improves mobility. We will  
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13 145 implement a modification of the intervention previously found to reduce frailty and improve  
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15 146 mobility in frail older people [16] to determine whether pre-frail participants receive similar  
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17 147 benefits with respect to frailty levels and mobility. To our knowledge this will be the first  
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19 148 study to examine the effects of an intervention specifically targeting degree of frailty among  
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21 149 older people who are pre-frail. The primary research question is: Does the multifactorial  
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23 150 interdisciplinary intervention prevent the progression to frailty (assessed with a frailty  
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25 151 phenotype score) and improve mobility among pre-frail older people, when compared with  
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27 152 usual care?  
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## 30 154 **METHODS AND DESIGN**

### 31 155 **Design**

32 156 A randomised controlled trial will be conducted among 230 participants who are pre-frail.  
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34 157 Figure 1 gives an overview of the study design. The Northern Sydney Local Health District  
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36 158 Health Research Ethics Committee approved this study (Research Protocol Number 1207-  
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38 159 213M) and all participants will give written informed consent prior to randomisation  
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40 160 (Appendix 1). The study is registered with the Australia New Zealand Clinical Trials Register  
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42 161 ACTRN12613000043730.  
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### 45 163 **Participants**

46  
47 164 Potential participants will be identified by clinicians working in hospital and community  
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49 165 sections of the Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-  
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51 166 ring-gai Health Service, in Sydney, Australia.  
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7 168 Participants who fulfill the following inclusion criteria will be invited to participate:

- 8 169 1. Male or female, aged 70 years or older  
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10 170 2. Meet one or two CHS frailty criteria,[17] and thus are considered pre-frail (Table 1)  
11  
12 171 3. Mild or no cognitive impairment (defined as a Mini Mental State Examination score >  
13 23);  
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16 173 People will be ineligible to participate in the trial if they:

- 17 174 1. Live in a residential aged care facility  
18  
19 175 2. Have an estimated life expectancy of less than 12 months (estimated by a score of  $\leq 3$   
20 176 on a modified version of the Implicit Illness Severity Scale [18])  
21  
22 177 3. Currently receive a treatment program from a rehabilitation facility  
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28 Table 1.

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Characteristic	Criteria
Weight loss/ Shrinking	Self-report of $\geq 4.5$ kg lost unintentionally in previous 12 months or loss of $\geq 5\%$ 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.
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### 181 **Randomisation**

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

188

### 189 **Allocation concealment**

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

196

### 197 **Intervention**

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

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7 201 medical management of health conditions, allied health input, assessment of care needs and  
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9 202 provision of care.

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12 204 Participants in the intervention group will receive an interdisciplinary, multifactorial  
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14 205 intervention for one year. The intervention will be individually tailored to each participant  
15  
16 206 based on the following: a) the CHS frailty characteristics present at baseline assessment; b)  
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18 207 additional problems identified during a detailed assessment by the physiotherapist providing  
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20 208 the intervention program, plus other relevant members of the interdisciplinary team; c)  
21  
22 209 ongoing reassessment by the interdisciplinary team throughout the intervention period. The  
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24 210 assessment and intervention will be underpinned by the principles of geriatric evaluation and  
25  
26 211 management.[20,21] An interdisciplinary team comprised of a physiotherapist, a geriatrician,  
27  
28 212 a rehabilitation physician, a dietician and a nurse will deliver the intervention. All  
29  
30 213 intervention staff will have experience in delivering interventions to older people. Case  
31  
32 214 management and regular case conferences will assist coordination of the interdisciplinary  
33  
34 215 delivery of the intervention. The treating physiotherapist will have the case coordinator role,  
35  
36 216 liaising with the participant, family, health professionals and service providers, plus  
37  
38 217 coordinating services as indicated.

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41 219 The intervention will be delivered primarily in participants' homes, with additional  
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43 220 community exercise programs and outpatient appointments (for example, podiatrist, memory  
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45 221 clinic, continence clinic) offered when indicated.

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49 223 The interventions targeting the CHS frailty characteristics are described below.

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7 225 *Weight loss*

8 226 A dietician will evaluate nutritional intake if the participant is not already effectively  
9 227 addressing their recent weight loss. If the participant's body mass index is <18.5 or mid  
10 228 upper arm circumference is < the 10<sup>th</sup> percentile (using Australian gender and age specific  
11 229 norms), nutritional supplementation will be offered using commercially available, high  
12 230 protein, high energy, supplements. Home delivered meals will be recommended if  
13 231 appropriate clinical criteria apply.  
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22 233 *Exhaustion*

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24 234 Referral to a psychiatrist or psychologist will be considered if the Geriatric Depression Scale  
25 235 score is high. Where the participant is socially isolated, opportunities to encourage greater  
26 236 social engagement will be identified, e.g. day activity groups, physical activity programs in  
27 237 the community, and telephone contact with volunteers.  
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34 239 *Grip weakness, slow four metre walk time, or low physical activity level*

35 240 A physiotherapist experienced in aged care will visit the participant's home ten times in the  
36 241 12 months study period. There will be five sessions in the first three months after  
37 242 randomisation, and five sessions over the following nine months. Visits will be 60 to 120  
38 243 minutes duration. The physiotherapist will prescribe a home exercise program to be  
39 244 performed for 20-30 minutes, up to six times per week, for 12 months. The exercises, degree  
40 245 of difficulty and number of repetitions prescribed will be based upon assessment of the  
41 246 individual participant's abilities. Lower limb balance and strengthening exercises will utilise  
42 247 the Weight Bearing Exercise for Better Balance (WEBB) program, available at  
43 248 [www.webb.org.au](http://www.webb.org.au).<sup>[22]</sup> The program targets strength and control of the lower limb extensor  
44 249 muscles (hip and knee extensors, ankle plantarflexors) with exercises including standing up  
45 250 from a chair, forward and lateral step-ups onto a block and heel raises whilst standing on a

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7 251 wedge. Resistance will be applied by body weight or by weighted vests or weight-belts as  
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9 252 appropriate. Balance will be targeted with exercises performed in standing with a  
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11 253 progressively narrowed base (feet together, tandem stance, single leg stance), stepping,  
12  
13 254 walking and reaching. Upper limb support will be minimised in order to adequately challenge  
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15 255 balance, but to ensure safety the environment will be set up with stable supports (e.g. bench  
16  
17 256 or table) close by that can be held as necessary. In addition, if upper limb weakness is  
18  
19 257 creating functional problems, then the physiotherapist may prescribe upper limb exercises  
20  
21 258 incorporating theraband or free weights for resistance. The physiotherapist will regularly  
22  
23 259 review and modify the optimal intensity and type of exercises for each participant to ensure  
24  
25 260 the intervention remains appropriate and challenging over the study period. We will  
26  
27 261 encourage family members or carers to assist with the exercise program when this is  
28  
29 262 indicated.

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31 264 Appropriate safe mobility programs will be prescribed if participants have low activity levels,  
32  
33 265 reduced endurance or specific functional goals. Feedback will be provided via monitoring of  
34  
35 266 distance/time or via a pedometer or *FitBit* (internet-linked pedometer). Participants will be  
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37 267 encouraged and supported in increasing their physical activity using exercise equipment that  
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39 268 they have at home, as well as community physical activity programs (such as Tai Chi or  
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41 269 strength and balance classes), community exercise facilities (such as gymnasiums and  
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43 270 swimming pools) and a return to past leisure activities such as golf and bowls.

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47 272 In addition to the interventions targeting the CHS frailty characteristics, individually-tailored  
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49 273 intervention will address additional problems identified during assessment. Intervention may  
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51 274 include, but will not be limited to, the following examples.

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7 276 | • General health status will be assessed and intervention tailored to each individual's  
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9 277 | problems. Where indicated, chronic disease management programs will be implemented  
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11 278 | or reinforced in conjunction with existing health services. We will use the principles of  
12  
13 279 | comprehensive geriatric assessment, with careful follow-up of chronic diseases, pain and  
14  
15 280 | conditions such as incontinence, osteoporosis and impaired cognition. The rehabilitation  
16  
17 281 | physician and geriatrician will play a central role in assessment and recommendations for ongoing  
18  
19 282 | intervention.
- 20 283 | • The rehabilitation physician or geriatrician will review medications used and will discuss  
21  
22 284 | any questionable medication use with the participant's general practitioner. Poor  
23  
24 285 | compliance with medications will be addressed by initiation or reinforcement of strategies  
25  
26 286 | such as education about medications, medication packaging in blister packs and reminder  
27  
28 287 | cards.
- 29 288 | • Referrals will be made as indicated to allied health, Hearing Australia, Vision Australia,  
30  
31 289 | and disease specific programs such as pulmonary rehabilitation, cardiac rehabilitation and  
32  
33 290 | Parkinson's Disease exercise classes.
- 34 291 | • The team will refer to agencies that provide assessments and provision of care and  
35  
36 292 | services. Examples are the Aged Care Assessment Team for assessment for packages of  
37  
38 293 | care, community nursing and service providers.
- 39 294 | • If transport is required, we will arrange referral to community transport services, taxi  
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41 295 | subsidy schemes and mobility parking schemes as appropriate.
- 42 296 | • Reduced social interaction will be targeted by facilitating attendance at community-based  
43  
44 297 | groups, day centres, clubs and exercise groups, as well as by arranging telephone contact  
45  
46 298 | with a volunteer.
- 47 299 | • We will advise on meal delivery services and frozen meals if this assistance is needed.
- 48 300 | • Mobility aids and other equipment will be recommended, obtained and set up where  
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50 301 | indicated. This may involve referral to an occupational therapist for environmental

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7 302 modifications.

8 303 • Advice on appropriate footwear will be provided if shoes are suboptimal.

9 304 • Ergonomic alterations will be made to optimise home office safety.

10 305 • If the participant is at risk of falling, they may be referred to falls-specific clinics (Falls  
11 306 and Osteoporosis Clinics) and programs (Stepping On program, Otago Exercise Program)  
12 307 available in the study area, in addition to the WEBB exercise program. Safety concerns  
13 308 will also be addressed with information about falls prevention, personal alarms and hip  
14 309 protectors.

15 310 • If the participant cares for another person or the participant has a carer who needs help,  
16 311 the carer's needs will be assessed and contact with Carers Australia will be suggested.

17 312  
18 313 The physiotherapist and participant will collaborate to set measurable goals within three  
19 314 months of recruitment. The goals will be based upon the CHS frailty characteristics present  
20 315 (such as goals relating to diet, functional consequences of weakness or amount of physical  
21 316 activity), or problems identified during geriatric assessment (such as establishing formal links  
22 317 with a diabetes educator, understanding medications or obtaining a care package). The goals  
23 318 will be documented, reviewed each session by the physiotherapist and participant, and new  
24 319 goals will be set when new issues are targeted.

25 320  
26 321 The physiotherapist will promote adherence to the intervention using strategies including  
27 322 goal setting, a flexible time-frame for intervention delivery, recording of exercise completion,  
28 323 and involvement of family and carers. In addition, programs will be tailored to suit individual  
29 324 requirements and interventions will be designed to be varied, sustainable and enjoyable.

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31 326 **Data collection**

32 327 Participants will undergo three home-based assessments. The baseline measures will be

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7 328 assessed prior to randomisation and further assessments will be conducted four and 12  
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9 329 months after randomisation. Additional health service utilisation data will be collected via a  
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11 330 telephone call at eight months. Blinded assessors (experienced health professionals) will  
12  
13 331 conduct follow-up assessments. To ensure blinding, participants will be instructed not to  
14  
15 332 disclose group allocation to the assessors. The assessors' perception of group allocation will  
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17 333 be assessed, to evaluate the success of assessor blinding.  
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20 335 **Outcome measures**

21  
22 336 Demographic and health information will be collected at baseline. Cognitive function will be  
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24 337 assessed with the Mini Mental State Examination.[23]

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28 339 - *Primary outcomes*

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30 340 The primary outcomes measured are frailty and mobility, measured at four and 12 months.  
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32 341 Frailty will be measured using the CHS frailty phenotype,[17] detailed in Table 1. The frailty  
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34 342 phenotype evaluates five components of the frailty syndrome and allocates one point for each  
35  
36 343 criterion met; participants meeting 0 criteria are defined as non-frail, 1 or 2 criteria are  
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38 344 defined as pre-frail, and 3, 4 or 5 criteria are defined as frail. Mobility will be assessed using  
39  
40 345 the lower extremity continuous summary performance score (CSPS),[24] with data collected  
41  
42 346 using the Short Physical Performance Battery (SPPB),[25] This battery examines the ability  
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44 347 to stand (for 10 sec) with the feet together in the side-by-side, semi-tandem, and tandem  
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46 348 positions, time taken to walk four metres, and time to rise from a chair and return to the  
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48 349 seated position five times.

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51 351 - *Secondary outcomes*

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53 352 1. Psychological status will be assessed using the five-item version of the Geriatric  
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55 353 Depression Scale.[26]

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7 354 2. Activities of daily living will be measured using the Barthel Index [27] (100 point  
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9 355 version). The mobility component of the Activity Measure for Post Acute Care [28] will  
10 356 measure self reported activity level using Item Response Theory and computer-adaptive  
11  
12 357 testing.
- 14 358 3. Gait speed will be measured using the four-metre walk test.
- 16 359 4. The EQ-5D (EuroQol) will measure health related quality of life and provide utility  
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18 360 weights to allow calculation of Quality adjusted life years (QALYs) for use in the  
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20 361 economic evaluation.[29]
- 22 362 5. Falls, hospitalisations and admissions to residential aged care facilities will be collected  
23  
24 363 via telephone at four, eight and 12 months and will also be used in the economic analyses.
- 26 364 6. Health and community service use will be recorded at four, eight and 12 months and will  
27  
28 365 be used in economic analyses.

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32 367 *- Additional measures*

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34 368 Adherence measurements will record the acceptance of health and other services by the study  
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36 369 participant. The treating physiotherapist will estimate a global level of adherence (in five  
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38 370 categories: 0%, <25%, 25-49%, 50-74% and  $\geq 75\%$ ) during the 12-month intervention. The  
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40 371 treating physiotherapist will evaluate goal attainment in the intervention group using a four-  
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42 372 point scale: deterioration from baseline ability, maintained baseline ability, goal met, goal  
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44 373 exceeded.

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47 375 Adverse events will be defined as medical events or injuries arising as a consequence of the  
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49 376 trial and resulting in medical attention or restricted activities of daily living for more than two  
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51 377 days.[30] Deaths will be documented.

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55 379 **Sample size calculation**

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7 380 An *a priori* power analysis determined 230 participants will need to be recruited, to provide  
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9 381 80% power to detect a clinically and statistically significant 15% between group difference in  
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11 382 lower extremity continuous summary performance score (SD = 0.7).[25] This sample size  
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13 383 will also provide sufficient power to detect a clinically meaningful 20% between-group  
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15 384 difference in transition to frailty. For these calculations, we assumed an  $\alpha$  of 0.05, non-  
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17 385 compliance of 15% and a dropout rate of 15%.

### 19 386 **Statistical analysis**

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21 387 Frailty will be treated as a dichotomous variable, scored as transitioned to frailty (that is, the  
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23 388 number of frailty criteria was 3 or more) or did not transition to frailty (number of frailty  
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25 389 criteria was 0, 1 or 2). The chi-square test will be used for frailty as a dichotomous variable.  
26  
27 390 The other study outcomes will be treated as continuous variables. The effect of group  
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29 391 allocation on continuously scored outcome measures at the four month and twelve month  
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31 392 follow-ups will be analysed using linear regression models with baseline scores entered into  
32  
33 393 the linear regression models as covariates. To aid interpretation of the change in frailty,  
34  
35 394 frailty will also be reported as a continuous variable. Statistical significance will be set at  
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37 395  $P < 0.05$  and we will report the differences in percentage or mean (95% confidence interval)  
38  
39 396 between the two groups at the 4-month and 12-month follow-ups.

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41 397 We will test whether the response to the intervention is modified by the number of frailty  
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43 398 criteria present at baseline, by including an interaction term of study groups with number of  
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45 399 frailty criteria at baseline in the regression analyses.[31] Secondary analyses will also explore  
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47 400 the effect of different rates of adherence (as a category variable: <25%, 25% to 49%, 50% to  
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49 401 74% and  $\geq 75\%$ ) on the outcomes in the intervention group at 12-month follow-up. We will  
50  
51 402 examine baseline variables and if there are important between group differences we will  
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53 403 adjust for them in the models. The primary analyses will be conducted in accordance with the  
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55 404 intention-to-treat principle.[32] Data will be coded to permit blinding to group allocation in

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7 405 the statistical analysis.

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9 406 Participants will be provided with their own results on request. The overall results will be  
10 407 available to participants once the final results are published. It is anticipated that participants  
11 408 will register their interest in receiving this information when their participation in the study  
12 409 ends.

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19 411 **Economic evaluation**

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21 412 The economic evaluation will be carried out and reported in accordance with health  
22 413 economics reporting standards.[33] The economic evaluation will take the perspective of  
23 414 Australian health and aged care service providers over a 12-month time period. Benefits will  
24 415 be measured in terms of number of transitions to frailty prevented, mobility improvement and  
25 416 QALYs gained (based on utility weights derived from the EQ-5D). The cost effectiveness  
26 417 analyses will include the cost of delivering the intervention and the cost of health and  
27 418 community service utilisation. Bootstrap sampling will be used to examine the joint  
28 419 probability distribution of costs and outcomes, with the creation of incremental cost-  
29 420 effectiveness planes and cost-effectiveness acceptability curves for each outcome.

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40 422 **Timeframe**

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42 423 Recruitment commenced in January 2013. Follow-up assessment is expected to conclude in  
43 424 October 2015.

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48 426 **DISCUSSION**

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50 427 This trial will provide important information to guide intervention to improve outcomes for  
51 428 older people who are pre-frail. Specifically, it will determine whether a multifactorial  
52 429 interdisciplinary intervention reduces transition to frailty and deterioration in mobility among  
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7 430 pre-frail older men and women who live in the community. Frailty and the associated  
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9 431 negative effects such as disability, institutionalisation and hospitalisation are costly to  
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11 432 individuals, their families, the health system and society. Despite this cost, to our knowledge  
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13 433 there has been no research to date examining the effectiveness of intervention designed to  
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15 434 reduce the transition to frailty among pre-frail older people.  
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18 436 The proposed multifactorial intervention will target the needs of each participant based upon  
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20 437 the characteristics of frailty present and comprehensive geriatric assessment. The exercise  
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22 438 component was designed using evidence from systematic reviews and randomised trials that  
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24 439 have demonstrated improved strength, balance and mobility in older people. We will  
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26 440 implement strategies to maximise adherence to the intervention, in line with research  
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28 441 suggesting good patient adherence increases the effectiveness of health interventions.[7,34]  
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30 442 The intervention is based on the program that was feasibly delivered to frail older people in  
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32 443 the Frailty Intervention Trial,[16] with some modifications to enable a greater challenge to  
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34 444 balance, strength and physical activity. Tailoring the exercises to the individual and ongoing  
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36 445 reassessment by the treating physiotherapist will ensure safety.  
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39 447 Additional strengths of the study are the generalisability to pre-frail older people and aged  
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41 448 care health service settings, and the robust, but pragmatic, clinical trial design. This study  
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43 449 uses an objective measure of pre-frailty; the CHS criteria have previously been used to recruit  
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45 450 frail [7] and pre-frail [13-15] people to clinical trials. We have avoided excessive exclusion  
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47 451 criteria. The intervention being examined is readily transferable to routine clinical practice in  
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49 452 the aged care health service setting and the interdisciplinary approach is relevant to several  
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51 453 professional groups in aged care.  
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55 455 This study has some limitations. First, participants cannot be blinded to group allocation,  
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7 456 which is a potential source of bias due to possible differential reporting of the weight loss,  
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9 457 activity and exhaustion frailty criteria. However, the weakness and slowness frailty criteria,  
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11 458 and the co-primary outcome measure (CSPS) are performance-based, which should reduce  
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13 459 this bias. Second, as there is no frequency-matched social intervention for the control group,  
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15 460 we will not be able to exclude the impact of social aspects of the program on any difference  
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17 461 between groups. Third, there is no consensus on how to identify pre-frailty [35] and while the  
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19 462 CHS phenotype is the most widely accepted instrument, other validated tools [36] and  
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21 463 attention to cognition could be considered in the clinical setting.  
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24 465 If this intervention is shown to be effective, there are major potential benefits to the older  
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26 466 population in terms of preventing transition to frailty and improving mobility. Avoiding  
27  
28 467 frailty has the potential to reduce adverse health outcomes, such as fall rates, hospitalisation  
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30 468 and institutionalisation, and the associated financial costs. Improved mobility may also result  
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32 469 in improved function and better quality of life for older people, their families and carers. If  
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34 470 cost-effectiveness is demonstrated, this intervention will lead to more efficient utilisation of  
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36 471 health services. The findings will be disseminated through scientific and professional  
37  
38 472 conferences, and in peer-reviewed journals.  
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#### 41 474 **List of abbreviations used**

42  
43 475 CHS: Cardiovascular Health Study

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45 476 Pre-FIT: Pre-Frailty Intervention Trial

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47 477 WEBB: Weight Bearing Exercise for Better Balance

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49 478 SPPB: Short Physical Performance Battery

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51 479 SD: standard deviation

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53 480 QALYs: Quality adjusted life years

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55 481 CSPS: lower extremity continuous summary performance score  
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20 489 **Competing Interests**

21  
22 490 The authors declare that they have no competing interests.

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24 49125  
26 492 **Authors' contributions**

27  
28 493 NF drafted the manuscript. All authors are actively involved in the study. All authors read  
29 494 and approved the final manuscript.

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34 496 **References**

- 35  
36 497 1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *Journal of the*  
37 498 *American Medical Directors Association* 2013;14(6):392-7.
- 38  
39 499 2. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward  
40 500 a better understanding of physiology and etiology: summary from the American Geriatrics  
41 501 Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am*  
42 502 *Geriatr Soc* 2006;54(6):991-1001.
- 43  
44 503 3. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J*  
45 504 *Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56.

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7 505 4. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and  
8  
9 506 comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*  
10  
11 507 2004;59(3):255-63.  
12  
13 508 5. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling  
14  
15 509 older persons: a systematic review. *Journal of the American Geriatrics Society*  
16  
17 510 2012;60(8):1487-92.  
18  
19 511 6. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for  
20  
21 512 the management of frailty: a systematic review. *J Aging Res* 2011;2011:569194.  
22  
23 513 7. Cameron ID, Fairhall N, Langron C, et al. A multifactorial interdisciplinary intervention  
24  
25 514 reduces frailty in older people: randomized trial. *BMC Med* 2013;11:65.  
26  
27 515 8. Gill TM, Gahbauer EA, Allore HG, et al. Transitions between frailty states among  
28  
29 516 community-living older persons. *Arch Intern Med* 2006;166(4):418-23.  
30  
31 517 9. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process.  
32  
33 518 *Gerontology* 2009;55(5):539-49.  
34  
35 519 10. Faber MJ, Bosscher RJ, Chin APMJ, et al. Effects of exercise programs on falls and  
36  
37 520 mobility in frail and pre-frail older adults: A multicenter randomized controlled trial. *Arch*  
38  
39 521 *Phys Med Rehabil* 2006;87(7):885-96.  
40  
41 522 11. Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in  
42  
43 523 physically frail, elderly persons who live at home. *N Engl J Med* 2002;347(14):1068-74.  
44  
45 524 12. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in  
46  
47 525 older people living in the community. *Cochrane Database Syst Rev* 2012(9):CD007146.  
48  
49 526 13. Daniel K. Wii-hab for pre-frail older adults. *Rehabil Nurs* 2012;37(4):195-201.  
50  
51 527 14. Lustosa LP, Silva JP, Coelho FM, et al. Impact of resistance exercise program on  
52  
53 528 functional capacity and muscular strength of knee extensor in pre-frail community-dwelling  
54  
55 529 older women: a randomized crossover trial. *Rev Bras Fisioter* 2011;15(4):318-24.  
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7 530 15. Coelho FM, Pereira DS, Lustosa LP, et al. Physical therapy intervention (PTI) increases  
8  
9 531 plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly  
10  
11 532 women. *Archives of gerontology and geriatrics* 2012;54(3):415-20.  
12  
13 533 16. Fairhall N, Aggar C, Kurrle SE, et al. Frailty Intervention Trial (FIT). *BMC Geriatrics*  
14  
15 534 2008;8:27.  
16  
17 535 17. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype.  
18  
19 536 *Journal of Gerontology* 2001;56A:M146-M56.  
20  
21 537 18. Holtzman J, Lurie N. Causes of increasing mortality in a nursing home population. *J Am*  
22  
23 538 *Geriatr Soc* 1996;44(3):258-64.  
24  
25 539 19. Beller EM, GebSKI V, Keech AC. Randomisation in clinical trials. *MJA*  
26  
27 540 2002;177(10):565-67.  
28  
29 541 20. Ko FC. The clinical care of frail, older adults. *Clin Geriatr Med* 2011;27(1):89-100.  
30  
31 542 21. Gallo JJ, Fulmer T, Paveza GJ, et al. *Handbook of Geriatric Assessment*. 3rd ed.  
32  
33 543 Maryland: Aspen Publishers, 2000.  
34  
35 544 22. Sherrington C. Exercise which challenges balance can prevent falls in older people: meta-  
36  
37 545 analysis of RCTs with meta-regression. *Australian Physiotherapy Association Conference*  
38  
39 546 *Week*. Cairns Australia, 2007.  
40  
41 547 23. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. "A practical method for  
42  
43 548 grading the cognitive state of patients for the clinician". *Journal of Psychiatric Research*  
44  
45 549 1975;12(3):189-98.  
46  
47 550 24. Onder G, Penninx BW, Lapuerta P, et al. Change in physical performance over time in  
48  
49 551 older women: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci*  
50  
51 552 2002;57(5):M289-93.  
52  
53 553 25. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery  
54  
55 554 assessing lower extremity function: association with self-reported disability and prediction of  
56  
57 555 mortality and nursing home admission. *Journal of gerontology* 1994;49(2):M85-94.

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7 556 26. Hoyle MT, Alessi CA, Harker JO, et al. Development and testing of a five-item version of  
8  
9 557 the Geriatric Depression Scale. *J Am Geriatr Soc* 1999;47(7):873-8.  
10  
11 558 27. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Maryland State*  
12  
13 559 *Medical Journal* 1965;14:61-65.  
14  
15 560 28. Haley SM, Coster WJ, Andres PL, et al. Score comparability of short forms and  
16  
17 561 computerized adaptive testing: Simulation study with the activity measure for post-acute  
18  
19 562 care. *Arch Phys Med Rehabil* 2004;85(4):661-6.  
20  
21 563 29. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group.  
22  
23 564 *Annals of Medicine* 2001;33(5):337-43.  
24  
25 565 30. Latham NK, Anderson CS, Lee A, et al. A randomized, controlled trial of quadriceps  
26  
27 566 resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in  
28  
29 567 Elderly Subjects (FITNESS). *J Am Geriatr Soc* 2003;51(3):291-9.  
30  
31 568 31. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine-reporting of subgroup  
32  
33 569 analyses in clinical trials. *N Engl J Med* 2007;357(21):2189-94.  
34  
35 570 32. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials*  
36  
37 571 2000;21(3):167-89.  
38  
39 572 33. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation  
40  
41 573 Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health  
42  
43 574 Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value*  
44  
45 575 *Health* 2013;16(2):231-50.  
46  
47 576 34. DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment  
48  
49 577 outcomes: a meta-analysis. *Med Care* 2002;40(9):794-811.  
50  
51 578 35. Abellan van Kan G, Rolland Y, Houles M, et al. The assessment of frailty in older adults.  
52  
53 579 *Clin Geriatr Med* 2010;26(2):275-86.  
54  
55 580 36. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty  
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57 581 in elderly people. *CMAJ* 2005;173(5):489-95.

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9 583 **Figures**

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11 584 **Figure 1.** Overview of the flow of participants through the Pre-frailty Intervention Trial

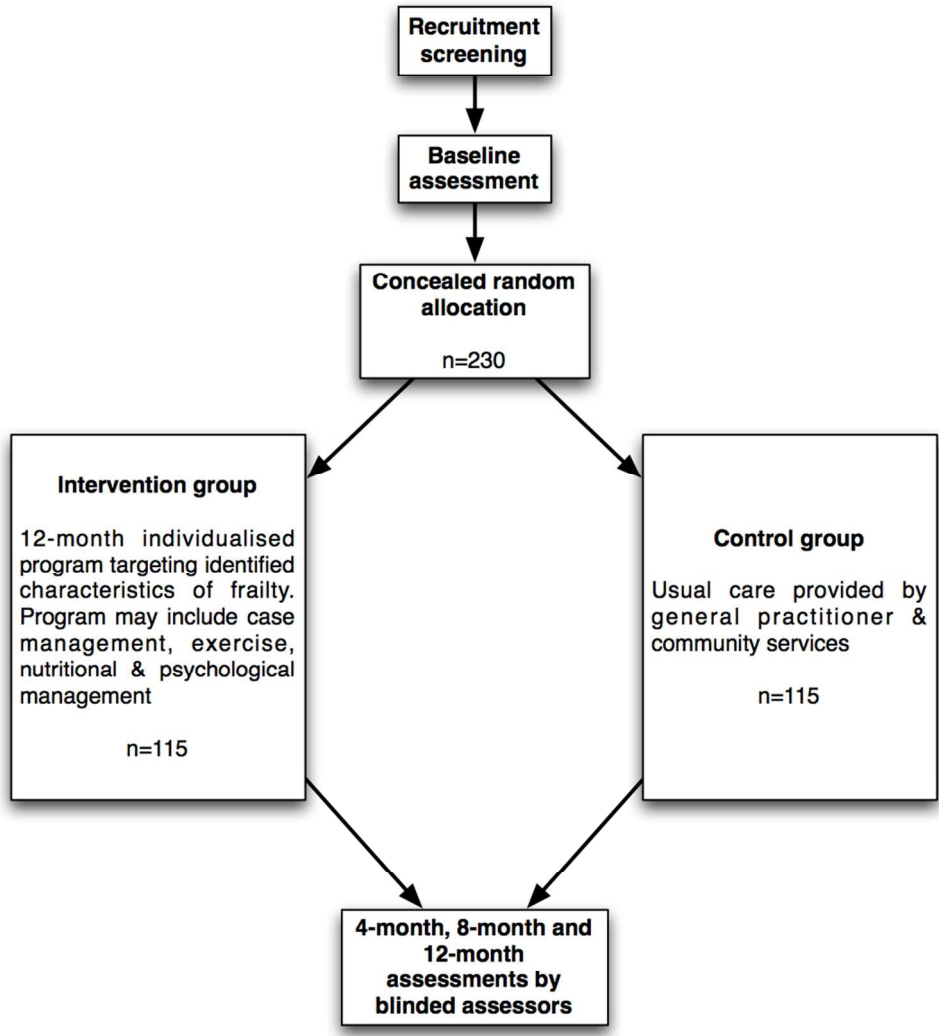
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13 585 **Appendix 1.** Informed consent form

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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. Slow 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.

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3 If you wish to withdraw from the study once it has started, you can do so at any  
4 time without having to give a reason.  
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#### 8 **4. What are the alternatives to participating in this study?**

9 If you decide not to participate in this study, you will still receive the standard  
10 treatment and care as would otherwise normally have been available to you in this  
11 area, generally accessible following consultation with your general practitioner.  
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#### 14 **5. What does this study involve?**

15 If you agree to participate in this study, you will be asked to sign the Participant  
16 Consent Form attached to this information sheet.  
17  
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19 This study will be conducted over a period of 12 months.  
20

21 This project is a randomised trial. If you agree to participate you will be put into  
22 one of two groups. One group will receive the multifactorial intervention while the  
23 other group will receive the 'usual care' that would otherwise have been available  
24 to them. Both groups will receive visits from our research team over a 12 month  
25 period. The results will be compared to see whether one treatment is more  
26 effective than the other. To ensure the groups are similar to start with, a computer  
27 allocates each study participant into a group randomly, like the flip of a coin.  
28 Neither the researcher nor the study participant can decide which group the  
29 participant will be allocated to. You will be told which group you are in.  
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32 All participants will be asked to complete three assessments with a study research  
33 nurse. One assessment is conducted at the commencement of the study, one  
34 after four months and the final assessment at the end of your involvement with the  
35 study (at 12 months). These assessments involve some minor strength and  
36 balance testing and some questions about your health, well being and service  
37 usage.  
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40 In addition, the researchers may require access to your hospital medical records in  
41 order  
42 to obtain information relevant to the study.  
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44

#### 45 **6. How is this study being paid for?**

46 The study is being sponsored by a trust fund connected to the Rehabilitation  
47 and Aged Care Service at Hornsby Ku-ring-gai Hospital. No money (besides  
48 normal salary) is paid directly to any individual researchers.  
49  
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#### 51 **7. Are there risks to me in taking part in this study?**

52 All medical procedures involve some risk of injury. In addition, there may be risks  
53 associated with this study that are presently unknown or unforeseeable. In spite of  
54 all reasonable precautions, it is possible you could develop a medical complication  
55 from participating in this study. Based on our experience there is a small risk that a  
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3 musculoskeletal symptom may develop as a result of the physical therapy  
4 intervention. This could be in the form of a muscular strain, or minor stress to  
5 ligaments or joint. In this unlikely event, the exercise program will be modified. There  
6 is also a slight risk of falling while exercising and this possibility will also be  
7 monitored.  
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### 10 11 12 13 **8. What happens if I suffer injury or complications as a result of the study?**

14 If you suffer any injuries or complications as a result of this study, you should  
15 contact the researcher visiting you as soon as possible, who will assist you in  
16 arranging appropriate medical treatment.  
17

18 You may have a right to take legal action to obtain compensation for any injuries  
19 or complications resulting from the study. Compensation may be available if your  
20 injury or complication is caused by the project intervention or by the negligence of  
21 any of the research staff who visit you. If you receive compensation that includes  
22 an amount for medical expenses, you will be required to pay for your medical  
23 treatment from those compensation monies.  
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26 If you are not eligible for compensation for your injury or complication under the  
27 law, but are eligible for Medicare, then you can receive any medical treatment  
28 required for your injury or complication free of charge as a public patient in any  
29 Australian public hospital.  
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### 32 33 **9. Will I benefit from the study?**

34 This study aims to further develop medical knowledge and may improve future  
35 treatment of frailty; it may or may not be of direct benefit you.  
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### 38 39 **10. Will taking part in this study cost me anything, and will I be paid?**

40 Participation in this study will not cost you anything; neither will you be paid for  
41 your participation.  
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### 44 45 **11. How will my confidentiality be protected?**

46 Any identifiable information that is collected about you in connection with this study  
47 will remain confidential and will be disclosed only with your permission, or as  
48 required by law. Only the study researchers will have access to your details and  
49 results and all information will be held securely at Hornsby Ku-ring-gai Hospital.  
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### 52 53 **12. What happens with the results?**

54 If you give us your permission by signing the consent document, we plan to publish  
55 the results of the study in peer reviewed journals at the conclusion of the trial. In  
56 any publication, information will be provided in such a way that you cannot be  
57 identified. Results of the study will be provided to you, if you wish.  
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4 **13. What happens to my treatment when the study is finished?**

5 If you are allocated to the group receiving the intervention, these visits will cease at  
6 the end of the study period. Usual community care, assessable through your  
7 general practitioner will resume at this point.  
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13 **14. What should I do if I want to discuss this study further before I decide?**

14 When you have read this information, the research nurse will discuss it with you  
15 and address any queries you may have. If you would like to know more at any  
16 stage, please do not hesitate to contact her or any member of the project team.  
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19  
20 **15. Who should I contact if I have concerns about the conduct of this study?**

21 This study has been approved by the Northern Sydney Coast Human Research  
22 ethics Committee of Northern Sydney and Central Coast Local Health Districts  
23 (NSLHD & CCLHD). Any person with concerns or complaints about the conduct of  
24 this study should contact Professor Ian Cameron at the Rehabilitation Studies Unit  
25 on (02) 9808-9236 or alternatively the Research Office on (02) 9926 8106 and  
26 quote "The Pre-frailty Intervention Trial" (Pre-FIT).  
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31 **Thank you for taking the time to consider this study.**  
32 **If you wish to take part in it, please sign the attached consent form.**  
33 **This information sheet is for you to keep.**  
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**Health**  
Northern Sydney  
Local Health District

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

1. I,.....  
  
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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.

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

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12 I understand that should I have a complaint in regards to the conduct of this trial it may  
13 be directed to either Professor Ian Cameron on telephone (02) 9808-9236 or the  
14 Northern Sydney Coast Human Research Ethics Committee on (02) 9926 8106.  
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18 **Signature of subject** **Please PRINT name** **Date**  
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27 **Signature of Researcher** **Please PRINT name** **Date**  
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**Health**  
Northern Sydney  
Local Health District

**Hornby Ku-ring-gai Health Service**

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

**REVOCAION 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
<b>Administrative information</b>			
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
<b>Introduction</b>			
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

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### 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:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	11
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those who	
7			enrol participants or assign interventions	
8				
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	11
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions	
12			are assigned	
13				
14	Implementation	16c	Who will generate the allocation sequence, who will enrol	11
15			participants, and who will assign participants to interventions	
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18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	11
19	(masking)		participants, care providers, outcome assessors, data analysts),	
20			and how	
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22		17b	If blinded, circumstances under which unblinding is permissible,	11
23			and procedure for revealing a participant's allocated intervention	
24			during the trial	
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27	<b>Methods: Data collection, management, and analysis</b>			
28				
29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	16,17
30	methods		other trial data, including any related processes to promote data	
31			quality (eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
35				
36		18b	Plans to promote participant retention and complete follow-up,	17
37			including list of any outcome data to be collected for participants	
38			who discontinue or deviate from intervention protocols	
39				
40				
41	Data	19	Plans for data entry, coding, security, and storage, including any	17
42	management		related processes to promote data quality (eg, double data entry;	
43			range checks for data values). Reference to where details of data	
44			management procedures can be found, if not in the protocol	
45				
46	Statistical	20a	Statistical methods for analysing primary and secondary	19,20
47	methods		outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
49				
50		20b	Methods for any additional analyses (eg, subgroup and adjusted	19,20
51			analyses)	
52				
53		20c	Definition of analysis population relating to protocol non-	20
54			adherence (eg, as randomised analysis), and any statistical	
55			methods to handle missing data (eg, multiple imputation)	
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**Methods: Monitoring**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	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**

25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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

1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	22
3	policy		participants, healthcare professionals, the public, and other	
4			relevant groups (eg, via publication, reporting in results	
5			databases, or other data sharing arrangements), including any	
6			publication restrictions	
7				
8		31b	Authorship eligibility guidelines and any intended use of	
9			professional writers	
10				
11		31c	Plans, if any, for granting public access to the full protocol,	n/a
12			participant-level dataset, and statistical code	
13				

### Appendices

14				
15				
16				
17	Informed consent	32	Model consent form and other related documentation given to	Appendix 1
18	materials		participants and authorised surrogates	
19				
20	Biological	33	Plans for collection, laboratory evaluation, and storage of	n/a
21	specimens		biological specimens for genetic or molecular analysis in the	
22			current trial and for future use in ancillary studies, if applicable	
23				

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.