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The EX-FRAIL CKD Trial: A Study Protocol for a Pilot Mixed-Methods Randomised Controlled Trial of a home-based EXercise programme for pre-FRAIL and FRAIL, older adults with Chronic Kidney Disease

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List of Abbreviations

CKD	Chronic Kidney Disease
FES-I	Falls Efficacy Scale-International
FP	Frailty Phenotype
HRQOL	Health-Related Quality of Life
LTHTR	Lancashire Teaching Hospitals NHS Foundation Trust
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute of Health Research
POS-S RENAL	Palliative Care Outcome Scale-Symptoms RENAL
RCT	Randomised Controlled Trial
SF-12	Short Form-12v2
SPPB	Short Physical Performance Battery

ABSTRACT

Introduction

Frailty is highly prevalent in adults with chronic kidney disease (CKD) and is associated with adverse health outcomes including falls, poorer health-related quality of life (HRQOL), hospitalisation and mortality. Low physical activity and muscle wasting are important contributors to physical frailty in adults with CKD. Exercise training may improve physical function and frailty status leading to associated improvements in health outcomes, including HRQOL. The EX-FRAIL CKD trial aims to inform the design of a definitive randomised controlled trial (RCT) that investigates the efficacy of a progressive, multi-component home-based exercise programme in pre-frail and frail older adults with CKD.

Methods and Analysis

The EX-FRAIL CKD trial is a mixed-methods, two-arm parallel group pilot RCT. Participants categorised as pre-frail or frail, following Frailty Phenotype assessment, will be randomised to receive exercise or usual care. Participants randomised to the intervention arm will receive a tailored 12-week exercise programme, which includes weekly telephone calls to advise on exercise progression. Primary feasibility outcome measures include rate of recruitment, intervention adherence, outcome measure completion and participant attrition. Semi-structured interviews with a purposively selected group of participants will inform the feasibility of the randomisation procedures, outcome measures and intervention. Secondary outcome measures include physical function (walking speed and Short Physical Performance Battery), frailty status (Frailty Phenotype), fall concern (Falls Efficacy Scale-International tool), activities of daily living (Barthel Index), symptom-burden (Palliative Care Outcome Scale-Symptoms RENAL) and HRQOL (Short Form-12v2).

Ethics and Dissemination

Ethical approval was granted by a National Health Service (NHS) Regional Ethics Committee and the NHS Health Research Authority. The study team aim to publish findings in a peer-reviewed journal and present the results at relevant national and international conferences. A summary of findings will be provided to participants, a local kidney patient charity and the funding body.

Trial Registration: ISRCTN87708989.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first pilot randomised controlled trial (RCT) to evaluate the feasibility of a progressive home-based exercise intervention specifically designed for pre-frail and frail older adults with chronic kidney disease (CKD).
- A validated assessment of frailty will be used to determine suitability for randomisation ensuring that only pre-frail and frail participants receive the intervention, thereby strengthening any conclusions that are made following study completion.
- The exercise programme is delivered in a graded and progressive manner with the use of weekly telephone calls to ensure safe exercise practices and provide ongoing encouragement.
- A nested qualitative study will explore the acceptability of the randomisation procedures, outcome measures and intervention, thus identifying areas for adaptation in a definitive RCT.
- Semi-structured interviews will be completed by a researcher involved in delivery of the study intervention, which may influence participant responses.

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INTRODUCTION

Frailty is the consequence of a cumulative decline in multiple physiological systems associated with ageing [1]. This results in a state of increased vulnerability to disproportionate changes in health status when exposed to seemingly minor insults, such as an infection or fall [1]. Frailty, and its precursor pre-frailty, are associated with an increased risk of falls, hospitalisation, worsening disability and death [2]. The pathophysiological process inherent to chronic kidney disease (CKD), including, though not limited to, uraemia, anabolic hormone dysregulation, increased inflammatory burden, metabolic acidosis and cellular senescence, appear to hasten the decline from fitness to frailty [3]. This is to such an extent that the prevalence of frailty in CKD, particularly by the time of dialysis initiation, is considerably greater than in the community-dwelling older adult population [4, 5]. Importantly, as in the general older population, patients with CKD and frailty have worse outcomes than their non-frail counterparts. Frailty is independently linked with adverse clinical outcomes in all stages of CKD, including an increased risk of worse health-related quality of life (HRQOL) [6, 7], falls [8], hospitalisation and mortality [9-11].

Low physical activity and associated muscle wasting are important contributors to physical frailty [12]. Physical activity is low in patients with advanced CKD [13] and muscle wasting is pronounced prior to the commencement of dialysis [14]. Increased physical activity levels in those with CKD and pre-frailty/frailty may mitigate this muscle wasting. Exercise training has been shown to improve physical fitness and HRQOL in CKD populations [15, 16]. However, patients living with frailty are typically poorly represented in interventional studies, often due to concerns that drop-out rates, adverse events or intervention tolerability may be affected [17, 18]. Studies that have explored the use of exercise training in frail older adults

have demonstrated benefits in terms of 'falls, mobility, balance, functional ability, muscle strength and body composition' [19]. However, the optimum exercise programme has not been established [19]. Regardless, exercise programmes that are effective for frail older adults may not meet the needs of patients living with frailty and CKD, who are more likely to be frail at a younger age [10], report considerable symptom burden [20] and have high health care utilisation [21].

Many exercise programmes used in studies involving participants with CKD have been performed under supervision within hospital or other facilities [15, 16], circumstances that can be challenging to implement in clinical practice considering financial and staffing constraints. Furthermore, travel for exercise sessions may be onerous for frail individuals with CKD who often report higher levels of fatigue [7]. Home-based exercise programmes may be less burdensome and more convenient, allowing patients to incorporate physical activity into their daily lives leading to longer term adoption and maintenance of increased physical activity [22]. There is evidence in the gerontology literature that home-based exercise interventions may improve disability in older people with frailty [23]. However, research is needed to evaluate the benefits of a pragmatic, progressive home-based exercise programme tailored to the needs of people living with frailty and CKD.

As recommended by the Medical Research Council (MRC) guidance for developing and evaluating complex interventions [24], pilot studies should be used to address key uncertainties prior to the definitive evaluation of complex interventions. Given the uncertainties previously described, a pilot mixed-methods randomised controlled trial (RCT) of a home-based exercise programme for pre-frail and frail older adults with CKD is

necessary. This will inform the design of a large-scale RCT that investigates the effect of a home-based exercise intervention on physical function, frailty status, fall concern, activities of daily living, symptom-burden and HRQOL in pre-frail and frail older adults with CKD. The 2013 SPIRIT guidelines [25, 26] will be used as the framework for reporting the EX-FRAIL CKD trial protocol.

Objectives

A pilot mixed-methods RCT will be performed that aims to:

1. Evaluate rate of participant recruitment, intervention adherence, outcome measure completion and attrition.
2. Qualitatively explore the acceptability of the randomisation procedure, outcome measures and, in the intervention arm, a progressive home-based exercise programme and identify areas requiring adaptation for a definitive RCT.
3. Estimate the standard deviation of walking speed in pre-frail and frail patients with CKD to allow sample size estimation for a definitive RCT.

METHODS AND ANALYSIS

Design

The EX-FRAIL CKD trial is a mixed-methods, two-arm parallel group pilot RCT. Outcome assessments will be performed at baseline and 12 weeks' post-randomisation. A nested-qualitative study will be performed following completion of 12-week follow-up visits to explore participant perceptions of the study and, where applicable, the study intervention.

Study Setting

Participants will be recruited from outpatient clinics at Lancashire Teaching Hospitals NHS Foundation Trust (LTHTR), East Lancashire Teaching Hospitals NHS Trust and Blackpool Teaching Hospitals NHS Foundation Trust. The regional nephrology service operates a 'hub and spoke' model, accordingly participants attending clinics at sites other than LTHTR are still under the care of the LTHTR nephrology service.

Inclusion Criteria

Patients aged ≥65 years old with CKD G3b-5 (not receiving dialysis or received a kidney transplant) identified as at least 'vulnerable' using the Clinical Frailty Scale (score ≥4) are eligible for participation [27]. The Clinical Frailty Scale is a 9-point scale that provides definitions for levels of frailty and has good diagnostic accuracy for identifying frailty in patients with advanced CKD [27, 28]. It has been adopted as a frailty screening measure within usual care and will maximise the likelihood of pre-frail and frail patients being approached for study involvement. Patients must also be able to give informed consent.

Exclusion Criteria

1. In accordance with the American College of Sport's Medicine [29]:
    - Unstable Angina or recent (within the last 3 months) myocardial infarction.
    - Uncontrolled arrhythmias.
    - Persistent uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
1. Recent (within the last 3 months) stroke or transient ischaemic attack.
2. Registered blind.
3. Unable to mobilise independently.
4. Receiving palliative care for advanced terminal cancer.
5. Recently (within the last 12 months) enrolled in a structured exercise programme (e.g. cardiac rehabilitation) prescribed by a health professional.
6. Anticipated to commence dialysis or receive a renal transplant within the next 3 months.
7. Insufficient understanding of the English language to complete study questionnaires or follow advice within the exercise programme guidebook.
8. Clinical and/or research team consider participation in the exercise programme unsafe.

Timeline

Figure 1 illustrates the participant flow through the study. Potentially eligible patients will be given a participant information sheet. Patients will then be telephoned to establish if they are interested in participating and to ensure eligibility. Patients will be offered an appointment with the Chief Investigator, at least 24 hours following the telephone call, to obtain written informed consent to participate in the study.

The Frailty Phenotype (FP) is currently considered the reference standard method to diagnose physical frailty in CKD populations [2, 5]. However, it is not routinely performed in clinical practice and therefore will only be performed following study consent. The FP includes 5 components, as detailed in Table 1 [2]. Frailty is diagnosed if an individual is assessed as having 3 components and pre-frailty if an individual has 1 or 2 components [2]. Participants will have a FP assessment pre-randomisation and will be withdrawn from the study if they are categorised as robust (i.e. not pre-frail or frail). Participants categorised as pre-frail or frail will be randomised to exercise or usual care groups and will complete all outcome assessments as detailed in Table 2. Follow-up outcome assessments will be performed 12-weeks post-randomisation. A group of participants will be invited to participate in semi-structured interviews following 12-week follow-up assessments.

Sample Size

We aim to recruit 40 participants to allow for a dropout rate (that includes participants categorised as robust using the FP) of up to 50% and still provide sufficient data to assess study feasibility and estimate the standard deviation of walking speed to inform the sample size calculation of a definitive RCT [30, 23, 19, 31]. Semi-structured interviews will be conducted with a purposively selected group of participants, from both study arms, considering age, gender and frailty status. A pragmatic sample size of 12-14 participants will be recruited to this nested qualitative study.

Allocation and Blinding

Participants will be randomised in a 1:1 ratio to either the intervention or usual care. A

central, concealed web-based randomisation process (www.sealedenvelope.com) will be performed in blocks of 4. Stratification will be limited to one factor, FP status, leaving 2 strata, i.e. pre-frailty and frailty [32]. This will ensure that both groups contain similar proportions of pre-frail and frail participants. Participants cannot be blinded to the outcome of randomisation due to the nature of the intervention. Furthermore, outcome assessors will not be blinded to the outcome of randomisation as this pilot study does not aim to evaluate intervention efficacy. Blinding of outcome assessors will be performed if a definitive RCT is considered feasible.

Intervention Development

The EX-FRAIL CKD exercise programme is a 12-week progressive, multi-component home-based exercise programme. It was developed through review of international guidance and systematic reviews that evaluated exercise interventions in CKD and older adult populations. A 2014 systematic review demonstrated that exercise training is associated with improved health outcomes in adults with CKD [16]. However, most studies evaluated interventions in adults with dialysis-dependent CKD and mostly aerobic exercise interventions [16]. The authors recommended further evaluation in non-dialysis populations and further analysis of resistance training and multi-component interventions [16]. Several systematic reviews have demonstrated that frail older adults benefit from exercise programmes and reported multi-component exercise programmes (involving combinations of strength, aerobic and balance training) were often effective [33, 34, 19]. A 2012 Cochrane review determined that both multi-component group exercise and home-based exercise reduce the rate of falls in older adults [35]. Furthermore, a systematic review of home-

based exercise programmes suggested that there is preliminary evidence that home-based exercise interventions may improve disability in older adults with moderate frailty [23]. The American College of Sports Medicine and American Heart Association Guidelines highlight the importance of physical activity being increased gradually in older adults, particularly those that are very deconditioned [36]. Additionally, the guidelines recommend that older adults who reduce their sedentary behaviour, even if not to the level recommended, still attain health benefits [36].

Intervention Description

Participants randomised to the intervention will receive an individual exercise education session delivered by a physiotherapist experienced in exercise prescription. Participants will be provided information about the potential benefits of physical activity for their general health and well-being. They will subsequently receive instruction on how to complete the exercises within the exercise programme safely and effectively. The exercises will be demonstrated to participants by a physiotherapist. The participants will then be asked to practice the exercises under supervision to ensure appropriate technique. If a participant is unable to perform a specific exercise, for example due to a functional limitation, an alternative will be provided that focuses on the same muscle groups. Furthermore, if a participant is unable to complete the proposed number of repetitions, the participant will be advised to perform a lower number of repetitions initially. This approach reflects exercise prescription in clinical practice and should increase the feasibility and safety of the exercise programme.

Table 3 demonstrates the six exercises within the programme and details the progressions for each exercise. Participants categorised as frail will initially be advised to perform each exercise at level 1, whereas participants categorised as pre-frail will be advised to perform each exercise at level 2, unless the physiotherapist determines that it would be unsafe for an individual participant to perform a specific exercise at this level. Participants will receive education on how to use the Borg rating of perceived exertion [37] and will be advised to perform exercise 1 at a light intensity (Borg score <12) and exercises 2-6 at a moderate intensity (Borg score 12-16). Participants will be asked to gradually increase physical activity levels so that they ultimately perform three exercise sessions at home per week, with each session lasting approximately 30-45 minutes. Participants will be provided an exercise guidebook comprising written guidance on each exercise with accompanying photographs of models demonstrating the exercises.

Participants will be encouraged to complete an exercise diary. The diary prompts participants to document each exercise session including when they exercised, if they completed all exercises, the duration to complete the full exercise session and their Borg rating of perceived exertion for each exercise completed. Participants randomised to the intervention will receive weekly telephone calls from the physiotherapist or a specialist trainee in renal medicine who has clinical and research experience with patients living with frailty and CKD. To enhance intervention fidelity, a telephone pro forma will be used that prompts a review of the participants exercise diary, exercise technique, any problems (including symptoms, falls and healthcare episodes), an exploration of any participant uncertainties about the exercise programme and goal-setting for the following week. The physiotherapist and specialist trainee will discuss the outcomes of telephone calls, as a

further safeguard of intervention fidelity. The telephone calls will be used to provide ongoing encouragement and to advise on exercise progression. If participants can perform exercises 2-6 comfortably (Borg score <12), the physiotherapist or specialist trainee will discuss exercise progression with the participant. If required, participants will be offered additional educational sessions during the 12-week intervention period to ensure safe exercise technique when progressing to more difficult exercise levels. Table 4 summarises the intervention using the Template for Intervention Description and Replication (TIDieR) checklist [38].

Patient and Public Involvement

The study was presented to the LTHTR Research Development Group, which includes lay members. Feedback from this meeting led to the adoption of a mixed-methods study design that included participant interviews. The proposed study was also presented to members of a local kidney patient charity, discussed in a patient focus group, supported by funding received from National Institute of Health Research (NIHR) Research Design Service, and with the LTHTR Lay Research Group, which is a group of local lay representatives. The study team were encouraged by positive feedback received on proposed study visits, outcome assessments and the exercise programme, including the burden of the intervention.

Primary Feasibility Outcome Measures

Primary feasibility outcome measures will be assessed as recommended by the CONSORT randomised pilot and feasibility trial guidelines [39]. The proportion of patients attending nephrology clinics that are eligible for study consent and the proportion of eligible patients subsequently recruited will be recorded. Reasons for ineligibility and non-consent will be

recorded. In the intervention arm, adherence will be assessed by telephoning participants weekly to review the preceding week's exercise activity and by reviewing participant exercise diaries at the end of the study period. Reasons for non-adherence will be documented. The proportion of participants who complete all outcome measures and who are lost to follow-up will be assessed. Reasons for failure to complete outcome measures and for study withdrawal will be recorded.

Using a predetermined topic guide, the specialist trainee will conduct semi-structured face-to-face interviews with participants. The interviews aim to explore the acceptability of the randomisation procedure, outcome measures and, in the intervention arm, a progressive home-based exercise programme. Perceived safety and barriers to participation will be explored. The interviews will be conducted in a private environment at the NIHR Lancashire Clinical Research Facility. Interviews will be audio recorded using a digital recorder with the participant's consent and will last approximately 30-60 minutes. Interviews will be transcribed verbatim.

A 'stop', 'change' and 'go' approach to progression criteria will be used as described in the literature [40], with qualitative data used to identify areas for adaptation for a definitive RCT if required. Table 5 details the study progression criteria.

Secondary Outcome Measures

1. Physical Function

Walking speed is independently associated with all-cause mortality in adults with CKD [41]. Walking speed will be assessed using infrared timing gates (Brower Timing System 2012,

Brower Timing Systems, Draper, UT, USA). Participants will be asked to walk 15 feet at their normal walking pace on two occasions, using their usual walking aid if applicable. The fastest of two assessments will be used for analysis. A meaningful change in walking speed has been described as 0.05 metres per second [42, 43].

The Short Physical Performance Battery (SPPB) comprises a group of measures of lower extremity function that together can be used to generate a composite score between 0 and 12 [44]. SPPB score is associated with mortality in adults with CKD [45]. A minimally significant change in SPPB has been reported as 0.5 points [42, 43]. The measures included in the SPPB are:

- Five chair stands: timed standing from a chair at a standardised height five times as quickly as able.
- Balance testing: stand in three positions with increasing difficulty (standing with feet side by side, in a semi-tandem position and in a full tandem position) for 10 seconds in each position.
- Walking speed: timed walking 8 feet at usual pace.

2. Frailty

As described earlier and detailed in Table 1, the FP can be used to diagnose pre-frailty and frailty [2], which are associated with adverse outcomes in CKD populations [9-11, 8, 6, 7]. Studies have not evaluated the change in frailty status following exercise interventions in CKD

populations. However, McAdams-DeMarco et al demonstrated an improvement in Frailty Phenotype score of 0.3 points following transplantation [46].

3. Activities of Daily Living

The Barthel Index evaluates independence with 10 activities of daily living to generate a score between 0 and 100 [47]. Higher scores indicate greater independence.

4. Falls

The Falls Efficacy Scale-International (FES-I) tool will be used to assess fall concern [48, 49]. It is a self-report questionnaire that asks individuals to rate their fall concern for 16 situations on a four-point scale. The answers are totalled to provide a cumulative score between 16 and 64. A score between 16 and 19 indicates low fall concern, between 20 and 27 moderate fall concern and between 28 and 64 high fall concern. The number of falls within the preceding 6 months will also be recorded.

5. Symptom-Burden

The Palliative Care Outcome Scale-Symptoms RENAL (POS-S RENAL) will be used to assess symptom burden [50]. The POS-S RENAL questionnaire asks individuals to report 17 symptoms that may have affected them over the preceding week and to indicate to what extent. Each symptom is scored and scores totalled to create a symptom-burden score with higher scores representing greater symptom-burden.

6. HRQOL

The Short Form-12v2 (SF-12) comprises 12 questions that are used to assess HRQOL [51, 52]. The answers are used to produce an 8-scale profile of health and well-being and to generate physical and mental health summary measures. Higher SF-12 scores represent better HRQOL. The proposed minimal important difference for SF-12 summary scales is 3 T-score points [53].

Data Management

All electronic study data will be recoded on a secure, password-protected database on the LTHTR server. The server is only be accessible using password-protected user profiles on LTHTR computers. Participant names and hospital identification numbers will not be recorded on this database; participants will be identified by a study-specific participant number. There will not be a formal data monitoring committee. However, data will be managed in accordance with the LTHTR Information Governance Policy.

Analysis Plan

As recommended by the 2010 CONSORT guidelines [39], feasibility quantitative outcome measures will be reported descriptively with 95% confidence intervals. This will include the proportion of eligible patients and recruited participants, participants who adhere to the intervention, participants who complete all outcome assessments and participants lost to follow-up. Secondary outcome measures will also be reported descriptively with 95% confidence intervals. The standard deviation of walking speed will be estimated for both trial arms to inform the sample size calculation for a definitive RCT. SPSS software (version 25, IBM Corp) will be used for statistical analysis.

Qualitative data will be analysed using thematic analysis whereby narrative segments will first be coded and then translated into more abstract themes in an iterative manner [54]. NVivo software (version 12.5.0, QSR International) will be used to support analysis. Two members of the researcher team will compare themes to ensure all codes are represented. Qualitative and quantitative findings will be linked to provide a more comprehensive understanding of trial and intervention acceptability.

Adverse Events

Serious adverse events are defined as any episode during the study period that requires inpatient hospitalisation, results in persistent/significant disability, is life threatening or results in death. All adverse events will be discussed with the medically-trained Chief Investigator who will assess seriousness and causality. All adverse events will be reported to the study sponsor and all suspected unexpected serious adverse reactions reported to the regional ethics committee. The trial will be stopped prematurely if three or more suspected unexpected serious adverse reactions occur.

Study Steering Committee

A study steering committee will provide scientific, ethical and financial oversight of research activity. The committee comprises clinicians, physiotherapists, academics, the study sponsor and a patient representative. Meetings will be held during before, during and on completion of the study. The patient representative will be remunerated as recommended by INVOLVE.

Ethics and Dissemination

Study ethical approval has been granted by the North West Greater Manchester East Research Ethics Committee (reference 18/NW/0211) and the National Health Service (NHS) Health Research Authority (project reference 244772). The LTHTR Centre for Health Research and Innovation accepted the role and responsibilities of study sponsorship. The study is subject to the LTHTR Internal Research and NIHR audit programmes to ensure all research activities are performed in accordance with the international standards of Good Clinical Practice, United Kingdom clinical trials legislation and trust policies. The trial is registered with the International Standard Randomised Controlled Trial Number Registry (ISRCTN87708989). Protocol amendments approved by the Research Ethics Committee/NHS Health Research Authority will be communicated with the study sponsor, study team and, where necessary, the trial registry.

The study dataset will not be made publicly available as it may be possible to identify participants from interview transcripts and as this pilot study does not aim to use quantitative data to demonstrate intervention efficacy. The study team aim to publish the findings in a peer-reviewed journal and present the results at national and international conferences. A summary of findings will be provided to participants, a local kidney patient charity and the funding body.

DISCUSSION

To our knowledge, the EX-FRAIL CKD trial is the first pilot RCT of a progressive home-based exercise intervention specifically designed for pre-frail and frail older adults with CKD. Given the uncertainties around recruitment rates, intervention adherence and outcome measure acceptability, it is necessary to perform a pilot study prior to proceeding with a full-scale trial. These uncertainties have been considered during study design, though amendments may be required to maximise the success of a multi-centre RCT.

This study's strengths include the use of a validated frailty screening measure [28] to assist participant recruitment and, during baseline assessment, the use of the reference standard for diagnosing physical frailty, i.e. the FP [2], to determine suitability for randomisation. This methodology will minimise the number of robust individuals approached for study consent and ensure that only pre-frail and frail participants receive the intervention, thereby strengthening any conclusions that can be made following study completion. Furthermore, the nested qualitative study will complement quantitative data analysis by exploring the acceptability of the randomisation procedures, outcome measures and intervention, thus identifying areas for adaptation in a definitive RCT. An acknowledged limitation is that semi-structured interviews will be completed by a researcher involved in delivery of the study intervention, which may influence participant responses. However, the participants will be encouraged to give honest responses by reinforcing that the study objectives include to explore the acceptability of the study and identify areas requiring adaptation for a definitive RCT.

Home-based exercise programmes have been performed safely in frail older adults [23], however, perceived safety concerns (e.g. fall concerns) may influence participant adherence to the exercise programme. Participants randomised to the intervention arm receive exercise education from a physiotherapist experienced in exercise prescription. Moreover, the exercise programme is delivered in a graded and progressive manner with the use of weekly telephone calls that ensure safe exercise practices, explore participant uncertainties and provide ongoing support. We hope that the above will minimise participant concerns, therefore maximising participant adherence to the exercise programme.

The EX-FRAIL CKD trial aims to inform the design of a definitive multi-centre RCT that explores the benefits of a progressive, multi-component home-based exercise programme. If a definitive RCT demonstrates improvements in the physical function of participants, associated improvements in mobility, fall concern, independence, symptom-burden and HRQOL are anticipated, supporting the case for a home-based exercise programme within routine clinical care.

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TABLES

Table 1. The Frailty Phenotype.

Frailty Phenotype Component	Measure
Unintentional Weight Loss	≥10 pounds or ≥5% body weight over the preceding 12 months.
Weakness	Hand grip strength will be assessed in the seated position with the elbow positioned at 90 degrees, supported by the arm of a chair, and with a hand-grip dynamometer (Takei 5101 GRIP-A dynamometer, Takei Scientific Inst. Co. Ltd., Niigata, Japan) supported by the assessor. Both arms will be examined with the highest score from three efforts from each side used for analysis. The body mass index and gender stratified hand grip strength cut-offs proposed by Fried et al are used to define weakness [2].
Slowness	Walking speed (15 feet) will be assessed as outlined in the section titled 'Physical Function'. The height and gender stratified walking speed cut-offs proposed by Fried et al are used to define slowness [2].
Low Physical Activity	A modified version of the Minnesota Leisure Time Questionnaire [55] will be used to assess physical activity. Low physical activity is defined as <383 kcal/wk for men and <270 kcals/wk for women [2].
Self-perceived Exhaustion	The CES-D Scale will be used to assess self-perceived exhaustion [56]. Participants will be read the following statements: (1) I felt that everything I did was an effort. (2) I could not get going. Participants will then be asked, 'How often in the last week did you feel this way?' and provided the following scale: 0 = rarely or none of the time, 1 = some of the time, 2 = moderate amount of the time, 3 = most of the time. Self-perceived exhaustion is defined as an answer ≥2 for either statement [2].
Frailty is diagnosed if 3 or more frailty components are present.	
Pre-frailty is diagnosed if 1 or 2 frailty components are present.	

kcal/wk, Kilocalories per week; CES-D, Center for Epidemiological Studies Depression.

Table 2. Schedule of Assessments

Assessment	Time		
	Screening	Baseline	Follow-Up
Clinical Frailty Scale	X		
Clinical Characteristics	X	X	
Weight, Height, HR, BP		X	X
Laboratory Variables	X	X	
Frailty Phenotype		X	X
SPPB		X	X
Barthel Index		X	X
SF-12		X	X
FES-I		X	X
POS-S RENAL		X	X
Semi-structured Interview			X

HR, Heart Rate; BP, Blood Pressure; SPPB, Short Physical Performance Battery; SF-12, Short Form-12v2; FES-I, Falls Efficacy Scale-International; POS-S RENAL, Palliative Care Outcome Scale-Symptoms RENAL.

Table 3. The EX-FRAIL CKD Exercise Programme.

Exercise	Level 1	Level 2	Level 3	Level 4
1. Walking	Walk for 1 minute	Walk for 2 minutes	Walk for 10 minutes	Walk for 15 minutes
2. Lower leg extension	Seated leg extension*	Seated leg raise*	Seated weighted (0.5kg) leg raise*	Seated weighted (1kg) leg raise*
3. Bilateral calf raises	Seated calf raises*	Standing calf raises placing hands on secure surface*	Standing calf raises placing finger tips on secure surface*	Standing calf raises*
4. Sit to stand	Sit to stand using arms to assist*	Sit to stand without using arms to assist*	Sit to stand holding 0.5kg weights*	Sit to stand holding 1kg weights*
5. Wall/table push up	Wall push up**	Wall push up*	Table push up**	Table push up*
6. Marching	Marching whilst seated*	Marching whilst standing with hands on secure surface*	Marching whilst standing*	Stair step*

*3 sets of 10 repetitions; **3 sets of 5 repetitions.

Table 4. TIDier Checklist.

Item		
1.	**Brief name**	The EX-FRAIL CKD Exercise Programme
2.	**Rationale**	Described in 'Introduction' and section titled 'Intervention Development'
3.	**Materials**	Exercise guidebook, exercise diary and wrist/ankle weights.
4.	**Procedures**	Described in section titled 'Intervention Description' and 'Participant Timeline'.
5.	**Provider**	Exercise programme education will be delivered by a physiotherapist experienced in exercise prescription. Weekly telephone calls will be performed by the physiotherapist or specialist trainee with relevant experience.
6.	**Modes of delivery**	Face-to-face exercise education session followed by weekly telephone calls.
7.	**Location**	Exercise education sessions will be delivered in a private room at NIHR Lancashire Clinical Research Facility. All exercise sessions will be completed in the participant's own home.
8.	**Frequency and duration**	All participants will have an exercise education session lasting approximately 60 minutes. Participants will aim to perform three exercise sessions at home per week, lasting approximately 30-45 minutes each.
9.	**Tailoring**	Initial exercise level will be determined by frailty status, unless the physiotherapist determines otherwise due to safety concerns. An alternative exercise will be provided if a participant is unable to perform a specific exercise as originally intended.
10.	**Modifications**	Cannot be described until study completion.
11.	**Adherence and fidelity: planned**	Exercises will be delivered as described in the exercise guidebook. If modification is needed, the participant (and study team) will be provided additional documentation. Adherence will be assessed during telephone calls and review of the participant's exercise diary. Outcomes of telephone calls will be discussed to maintain fidelity.
12.	**Adherence and fidelity: actual**	Cannot be described until study completion.

NIHR, National Institute of Health Research.

Table 5. Progression Criteria.

Progression Criteria	Stop/Go Thresholds
Eligibility	**STOP:** <5% of patients eligible **GO:** >10% of patients eligible
Recruitment	**STOP:** <10% of eligible patients recruited **GO:** >30% of eligible patients recruited
Exercise Adherence **(defined as ≥2 sessions/week)**	**STOP:** <30% adherence **GO:** >70% adherence
Outcome Measure Completion **(not including lost to follow up)**	**STOP:** <70% outcome measure completion **GO:** >80% outcome measure completion
Loss to Follow-Up **(including withdrawn and lost)**	**STOP:** >50% loss to follow-up **GO:** <25% loss to follow-up

FIGURE LEGEND

Figure 1. Study Flow-Diagram.

AUTHORS CONTRIBUTIONS

All authors contributed to the design of the study and writing of the protocol. ACN, TMB, HJG, and HMLY were involved in the development of the EX-FRAIL CKD exercise programme.

FUNDING STATEMENT

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COMPETING INTERESTS STATEMENT

Unrelated to this body of work, APD has received lecture fees from speaking at the invitation of MSD and received travel support from Pharmacosmos.

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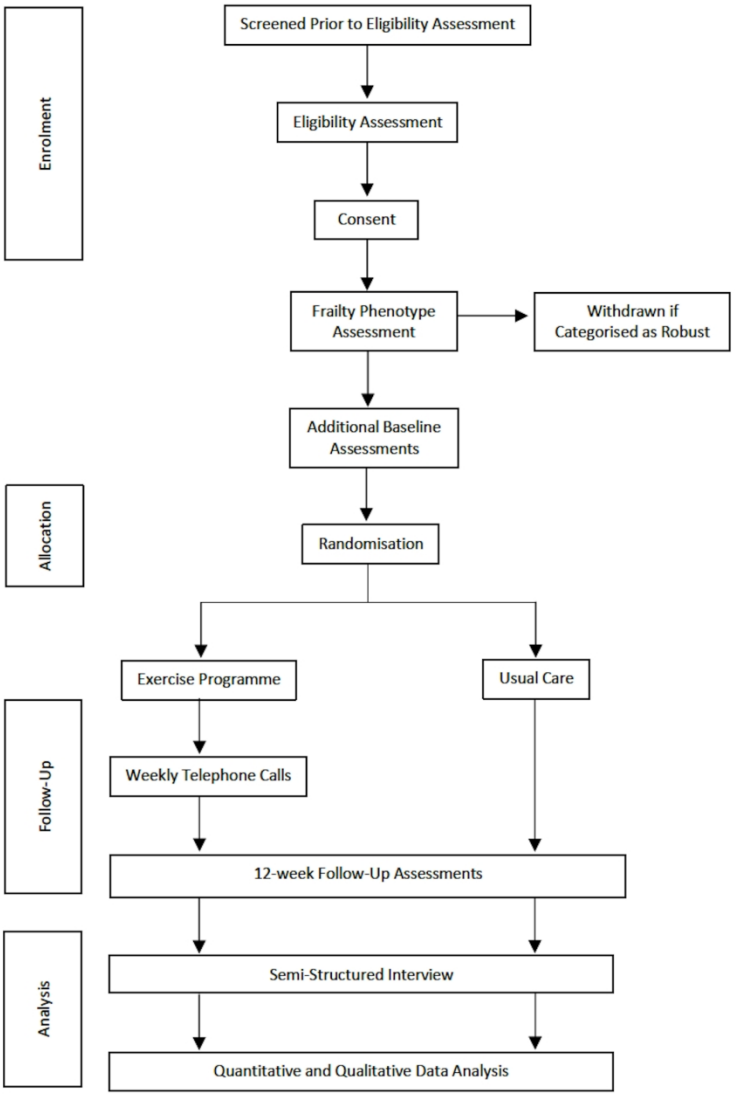

Figure 1. Study Flow-Diagram.

Figure 1. Study Flow-Diagram.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1,5
	2b	All items from the World Health Organization Trial Registration Data Set	7-24
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	38
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	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	38
	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)	21

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9, 13-14
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
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	10
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-16
	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)	14-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	16-20
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)	11-12

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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12-13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12-13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13, 16-20

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21-22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21-22
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)	22

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	
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	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	38
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	
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	
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	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

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

BMJ Open

The EX-FRAIL CKD Trial: a study protocol for a pilot randomised controlled trial of a home-based EXercise programme for pre-FRAIL and FRAIL, older adults with Chronic Kidney Disease

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Geriatric medicine, Sports and exercise medicine, Rehabilitation medicine, Qualitative research, Research methods
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The EX-FRAIL CKD Trial: a study protocol for a pilot randomised controlled trial of a home-based EXercise programme for pre-FRAIL and FRAIL, older adults with Chronic Kidney Disease

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List of Abbreviations

CKD	Chronic Kidney Disease
FES-I	Falls Efficacy Scale-International
FP	Frailty Phenotype
HRQOL	Health-Related Quality of Life
LTHTR	Lancashire Teaching Hospitals NHS Foundation Trust
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute of Health Research
POS-S RENAL	Palliative Care Outcome Scale-Symptoms RENAL
RCT	Randomised Controlled Trial
SF-12	Short Form-12v2
SPPB	Short Physical Performance Battery

ABSTRACT

Introduction

Frailty is highly prevalent in adults with chronic kidney disease (CKD) and is associated with adverse health outcomes including falls, poorer health-related quality of life (HRQOL), hospitalisation and mortality. Low physical activity and muscle wasting are important contributors to physical frailty in adults with CKD. Exercise training may improve physical function and frailty status leading to associated improvements in health outcomes, including HRQOL. The EX-FRAIL CKD trial aims to inform the design of a definitive randomised controlled trial (RCT) that investigates the effectiveness of a progressive, multi-component home-based exercise programme in pre-frail and frail older adults with CKD.

Methods and Analysis

The EX-FRAIL CKD trial is a two-arm parallel group pilot RCT. Participants categorised as pre-frail or frail, following Frailty Phenotype assessment, will be randomised to receive exercise or usual care. Participants randomised to the intervention arm will receive a tailored 12-week exercise programme, which includes weekly telephone calls to advise on exercise progression. Primary feasibility outcome measures include rate of recruitment, intervention adherence, outcome measure completion and participant attrition. Semi-structured interviews with a purposively selected group of participants will inform the feasibility of the randomisation procedures, outcome measures and intervention. Secondary outcome measures include physical function (walking speed and Short Physical Performance Battery), frailty status (Frailty Phenotype), fall concern (Falls Efficacy Scale-International tool), activities of daily living (Barthel Index), symptom-burden (Palliative Care Outcome Scale-Symptoms RENAL) and HRQOL (Short Form-12v2).

Ethics and Dissemination

Ethical approval was granted by a National Health Service (NHS) Regional Ethics Committee and the NHS Health Research Authority. The study team aim to publish findings in a peer-reviewed journal and present the results at relevant national and international conferences. A summary of findings will be provided to participants, a local kidney patient charity and the funding body.

Trial Registration: ISRCTN87708989.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A validated frailty assessment will be used to determine suitability for randomisation ensuring that only pre-frail and frail participants receive the intervention.
- The exercise programme is delivered in a graded and progressive manner with the use of weekly participant telephone calls to review progress.
- A nested qualitative study will explore the acceptability of the randomisation procedures, outcome measures and intervention to participants.
- Semi-structured interviews will be completed by a researcher involved in delivery of the study intervention.
- Patients that decline study enrolment will not be offered the opportunity to participate in the qualitative study.

INTRODUCTION

Frailty is the consequence of a cumulative decline in multiple physiological systems associated with ageing [1]. This results in a state of increased vulnerability to disproportionate changes in health status when exposed to seemingly minor insults, such as an infection or fall [1]. Frailty, and its precursor pre-frailty, are associated with an increased risk of falls, hospitalisation, worsening disability and death [2]. The pathophysiological process inherent to chronic kidney disease (CKD), including, though not limited to, uraemia, anabolic hormone dysregulation, increased inflammatory burden, metabolic acidosis and cellular senescence, appear to hasten the decline from fitness to frailty [3]. This is to such an extent that the prevalence of frailty in CKD, particularly by the time of dialysis initiation, is considerably greater than in the community-dwelling older adult population [4,5]. Importantly, as in the general older population, patients with CKD and frailty have worse outcomes than their non-frail counterparts. Frailty is independently linked with adverse clinical outcomes in all stages of CKD, including an increased risk of worse health-related quality of life (HRQOL) [6,7], falls [8], hospitalisation and mortality [9-11].

Low physical activity and associated muscle wasting are important contributors to physical frailty [3]. Physical activity is low in patients with advanced CKD [12] and muscle wasting is pronounced prior to the commencement of dialysis [13]. Increased physical activity levels in those with CKD and pre-frailty/frailty may mitigate this muscle wasting. Exercise training has been shown to improve physical fitness and HRQOL in CKD populations [14,15]. However, patients living with frailty are typically poorly represented in interventional studies, often due to concerns that drop-out rates, adverse events or intervention tolerability may be affected [16,17]. Studies that have explored the use of exercise training in frail older adults

have demonstrated benefits in terms of 'falls, mobility, balance, functional ability, muscle strength and body composition' [18]. However, the optimum exercise programme has not been established [18]. Regardless, exercise programmes that are effective for frail older adults may not meet the needs of patients living with frailty and CKD, who are more likely to be frail at a younger age [10], report considerable symptom burden [19] and have high health care utilisation [20].

Many exercise programmes used in studies involving participants with CKD have been performed under supervision within hospital or other facilities [14,15], circumstances that can be challenging to implement in clinical practice considering financial and staffing constraints. Furthermore, travel for exercise sessions may be onerous for frail individuals with CKD who often report higher levels of fatigue [6]. Home-based exercise programmes may be less burdensome and more convenient, allowing patients to incorporate physical activity into their daily lives leading to longer term adoption and maintenance of increased physical activity [21]. There is evidence in the gerontology literature that home-based exercise interventions may improve disability in older people with frailty [22]. However, research is needed to evaluate the benefits of a pragmatic, progressive home-based exercise programme tailored to the needs of people living with frailty and CKD.

As recommended by the Medical Research Council (MRC) guidance for developing and evaluating complex interventions [23], pilot studies should be used to address key uncertainties prior to the definitive evaluation of complex interventions. Given the uncertainties previously described, a pilot randomised controlled trial (RCT) of a home-based exercise programme for pre-frail and frail older adults with CKD is necessary. This will

inform the design of a large-scale RCT that investigates the effect of a home-based exercise intervention on physical function, frailty status, fall concern, activities of daily living, symptom-burden and HRQOL in pre-frail and frail older adults with CKD. The 2013 SPIRIT guidelines [24,25] will be used as the framework for reporting the EX-FRAIL CKD trial protocol.

Objectives

A pilot RCT will be performed that aims to:

1. Evaluate rate of participant recruitment, intervention adherence, outcome measure completion and attrition.
2. Qualitatively explore the acceptability of the randomisation procedure, outcome measures and, in the intervention arm, a progressive home-based exercise programme and identify areas requiring adaptation for a definitive RCT.
3. Estimate the standard deviation of walking speed in pre-frail and frail patients with CKD to allow sample size estimation for a definitive RCT.

METHODS AND ANALYSIS

Design

The EX-FRAIL CKD trial is a two-arm parallel group pilot RCT. Outcome assessments will be performed at baseline and 12 weeks' post-randomisation. A nested-qualitative study will be performed following completion of 12-week follow-up visits to explore participant perceptions of the study and, where applicable, the study intervention.

Study Setting

Participants will be recruited from outpatient clinics at Lancashire Teaching Hospitals NHS Foundation Trust (LTHTR), East Lancashire Teaching Hospitals NHS Trust and Blackpool Teaching Hospitals NHS Foundation Trust. The regional nephrology service operates a 'hub and spoke' model, accordingly participants attending clinics at sites other than LTHTR are still under the care of the LTHTR nephrology service.

Inclusion Criteria

Patients aged ≥65 years old with CKD G3b-5 (not receiving dialysis or received a kidney transplant) identified as at least 'vulnerable' using the Clinical Frailty Scale (score ≥4) are eligible for participation [26]. The Clinical Frailty Scale is a 9-point scale that provides definitions for levels of frailty and has good diagnostic accuracy for identifying patients with advanced CKD at risk of frailty [26,27]. It has been adopted as a frailty screening measure within usual care at LTHTR and is used by clinicians and clinical nurse specialists in outpatient clinics. Using a Clinical Frailty Scale score ≥4 within the inclusion criteria will maximise the likelihood of pre-frail and frail patients being approached for study involvement. Patients must also be able to give informed consent.

Exclusion Criteria

1. In accordance with the American College of Sport's Medicine [28]:
    - Unstable Angina or recent (within the last 3 months) myocardial infarction.
    - Uncontrolled arrhythmias.
    - Persistent uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
2. Recent (within the last 3 months) stroke or transient ischaemic attack.
3. Registered blind.
4. Unable to mobilise independently.
5. Receiving palliative care for advanced terminal cancer.
6. Recently (within the last 12 months) enrolled in a structured exercise programme (e.g. cardiac rehabilitation) prescribed by a health professional.
7. Anticipated to commence dialysis or receive a renal transplant within the next 3 months.
8. Insufficient understanding of the English language to complete study questionnaires or follow advice within the exercise programme guidebook.
9. Clinical and/or research team consider participation in the exercise programme unsafe.

Timeline

Figure 1 illustrates the participant flow through the study. Patients will be screened by members of the clinical team (based on age, CKD stage and Clinical Frailty Scale score). Patients aged ≥65 years with CKD G3b-5 and a Clinical Frailty Scale score ≥4 will be given a

participant information sheet. Patients will then be telephoned to establish if they are interested in participating and to ensure eligibility. Patients will be offered an appointment with the Chief Investigator, at least 24 hours following the telephone call, to obtain written informed consent to participate in the study.

Our previous study demonstrated that a Clinical Frailty Scale score ≥4 had a sensitivity and specificity for identifying frailty of 1.00 and 0.55, respectively [27]. Given the risk of false positives, we considered it prudent to perform a more objective frailty assessment to ensure that only patients with pre-frailty or frailty underwent randomisation. The Frailty Phenotype (FP) is a well-studied method to diagnose physical frailty in CKD populations [2,5]. The FP includes 5 components, as detailed in Table 1 [2]. Frailty is diagnosed if an individual is assessed as having 3 components and pre-frailty if an individual has 1 or 2 components [2]. The FP is not routinely performed in clinical practice and therefore can only be performed following study consent. Participants will have a FP assessment pre-randomisation and will be withdrawn from the study if they are categorised as robust (i.e. not pre-frail or frail). This eventuality will be explained to patients prior to study consent. Participants categorised as pre-frail or frail will complete all outcome assessments as detailed in Table 2 and then be randomised to exercise or usual care groups. Follow-up outcome assessments will be performed 12-weeks post-randomisation. A group of participants will be invited to participate in semi-structured interviews following 12-week follow-up assessments (or following a participant's decision to stop the exercise programme).

Sample Size

We aim to recruit 40 participants to allow for a dropout rate (that includes participants categorised as robust using the FP) of up to 50% and still provide sufficient data to assess study feasibility and estimate the standard deviation of walking speed to inform the sample size calculation for a definitive RCT [18,22,29,30]. Semi-structured interviews will be conducted with a purposively selected group of participants, from both study arms, considering age, gender and frailty status. A pragmatic sample size of 12-14 participants will be recruited to this nested qualitative study.

Allocation and Blinding

Participants will be randomised in a 1:1 ratio to either the intervention or usual care. A central, concealed web-based randomisation process (www.sealedenvelope.com) will be performed in blocks of 4. Stratification will be limited to one factor, FP status, leaving 2 strata, i.e. pre-frailty and frailty [31]. This will ensure that both groups contain similar proportions of pre-frail and frail participants. Participants cannot be blinded to the outcome of randomisation due to the nature of the intervention. Furthermore, outcome assessors will not be blinded to the outcome of randomisation as this pilot study does not aim to evaluate intervention effectiveness. Blinding of outcome assessors will be performed if a definitive RCT is considered feasible.

Intervention Development

The EX-FRAIL CKD exercise programme is a 12-week progressive, multi-component home-based exercise programme. It was developed through review of international guidance and systematic reviews that evaluated exercise interventions in CKD and older adult

populations. A 2014 systematic review demonstrated that exercise training is associated with improved health outcomes in adults with CKD [15]. However, most studies evaluated interventions in adults with dialysis-dependent CKD and mostly aerobic exercise interventions [15]. The authors recommended further evaluation in non-dialysis populations and further analysis of resistance training and multi-component interventions [15]. Several systematic reviews have demonstrated that frail older adults benefit from exercise programmes and reported multi-component exercise programmes (involving combinations of strength, aerobic and balance training) were often effective [18,32,33]. A 2012 Cochrane review determined that both multi-component group exercise and home-based exercise reduce the rate of falls in older adults [34]. Furthermore, a systematic review of home-based exercise programmes suggested that there is preliminary evidence that home-based exercise interventions may improve disability in older adults with moderate frailty [22]. The American College of Sports Medicine and American Heart Association Guidelines highlight the importance of physical activity being increased gradually in older adults, particularly those that are very deconditioned [35]. Additionally, the guidelines recommend that older adults who reduce their sedentary behaviour, even if not to the level recommended, still attain health benefits [35].

Intervention Description

Participants randomised to the intervention will receive an individual exercise education session delivered by a physiotherapist experienced in exercise prescription. Participants will be provided information about the potential benefits of physical activity for their general health and well-being. They will subsequently receive instruction on how to complete the

exercises within the exercise programme safely and effectively. The exercises will be demonstrated to participants by a physiotherapist. The participants will then be asked to practice the exercises under supervision to ensure appropriate technique. If a participant is unable to perform a specific exercise, for example due to a functional limitation, an alternative will be provided that focuses on the same muscle groups. Furthermore, if a participant is unable to complete the proposed number of repetitions, the participant will be advised to perform a lower number of repetitions initially. This approach reflects exercise prescription in clinical practice and should increase the feasibility and safety of the exercise programme.

Table 3 demonstrates the six exercises within the programme and details the progressions for each exercise. Participants categorised as frail will initially be advised to perform each exercise at level 1, whereas participants categorised as pre-frail will be advised to perform each exercise at level 2, unless the physiotherapist determines that it would be unsafe for an individual participant to perform a specific exercise at this level. Participants will receive education on how to use the Borg rating of perceived exertion [36] and will be advised to perform exercise 1 at a light intensity (Borg score <12) and exercises 2-6 at a moderate intensity (Borg score 12-16). Participants will be asked to gradually increase physical activity levels so that they ultimately perform three exercise sessions at home per week, with each session lasting approximately 30-45 minutes. Participants will be provided an exercise guidebook comprising written guidance on each exercise with accompanying photographs of models demonstrating the exercises.

Participants will be encouraged to complete an exercise diary. The diary prompts participants to document each exercise session including when they exercised, if they completed all exercises, the duration to complete the full exercise session and their Borg rating of perceived exertion for each exercise completed. Participants randomised to the intervention will receive weekly telephone calls from the physiotherapist or a specialist trainee in renal medicine who has clinical and research experience with patients living with frailty and CKD. To enhance intervention fidelity, a telephone pro forma will be used that prompts a review of the participants exercise diary, exercise technique, any problems (including symptoms, falls and healthcare episodes), an exploration of any participant uncertainties about the exercise programme and goal-setting for the following week. The physiotherapist and specialist trainee will discuss the outcomes of telephone calls, as a further safeguard of intervention fidelity. The telephone calls will be used to provide ongoing encouragement and to advise on exercise progression. If participants can perform exercises 2-6 comfortably (Borg score <12), the physiotherapist or specialist trainee will discuss exercise progression with the participant. If required, participants will be offered additional educational sessions during the 12-week intervention period to ensure safe exercise technique when progressing to more difficult exercise levels. Figure 2 illustrates the exercise intervention logic model and Table 4 summarises the intervention using the Template for Intervention Description and Replication (TIDieR) checklist [37].

Patient and Public Involvement

The study was presented to the LTHTR Research Development Group, which includes lay members. Feedback from this meeting led to the adoption of a study design that included a nested qualitative interview study. The proposed study was also presented to members of a

local kidney patient charity, discussed in a patient focus group, supported by funding received from National Institute of Health Research (NIHR) Research Design Service, and with the LTHTR Lay Research Group, which is a group of local lay representatives. The study team were encouraged by positive feedback received on proposed study visits, outcome assessments and the exercise programme, including the burden of the intervention.

Primary Feasibility Outcome Measures

Primary feasibility outcome measures will be assessed as recommended by the CONSORT randomised pilot and feasibility trial guidelines [38]. The proportion of patients attending nephrology clinics that are eligible for study consent and the proportion of eligible patients subsequently recruited will be recorded. Reasons for ineligibility and non-consent will be recorded. In the intervention arm, adherence will be assessed by telephoning participants weekly to review the preceding week's exercise activity and by reviewing participant exercise diaries at the end of the study period. Reasons for non-adherence will be documented. The proportion of participants who complete all outcome measures and who are lost to follow-up will be assessed. Reasons for failure to complete outcome measures and for study withdrawal will be recorded.

Using a predetermined topic guide, the specialist trainee will conduct semi-structured face-to-face interviews with participants. The interviews aim to explore the acceptability of the randomisation procedure, outcome measures and, in the intervention arm, a progressive home-based exercise programme. Perceived safety and barriers to participation will be explored. The interviews will be conducted in a private environment at the NIHR Lancashire Clinical Research Facility. Interviews will be audio recorded using a digital recorder with the

participant's consent and will last approximately 30-60 minutes. Interviews will be transcribed verbatim.

A 'stop', 'change' and 'go' approach to progression criteria will be used as described in the literature [39], with qualitative data used to identify areas for adaptation for a definitive RCT if required. Table 5 details the study progression criteria.

Secondary Outcome Measures

1. Physical Function

Walking speed is independently associated with all-cause mortality in adults with CKD [40]. Walking speed will be assessed using infrared timing gates (Brower Timing System 2012, Brower Timing Systems, Draper, UT, USA). Participants will be asked to walk 15 feet at their normal walking pace on two occasions, using their usual walking aid if applicable. The fastest of two assessments will be used for analysis. A meaningful change in walking speed has been described as 0.05 metres per second [41,42].

The Short Physical Performance Battery (SPPB) comprises a group of measures of lower extremity function that together can be used to generate a composite score between 0 and 12 [43]. SPPB score is associated with mortality in adults with CKD [44]. A minimally significant change in SPPB has been reported as 0.5 points [41,42]. The measures included in the SPPB are:

- Five chair stands: timed standing from a chair at a standardised height five times as quickly as able.

- Balance testing: stand in three positions with increasing difficulty (standing with feet side by side, in a semi-tandem position and in a full tandem position) for 10 seconds in each position.
- Walking speed: timed walking 8 feet at usual pace.

2. Frailty

As described earlier and detailed in Table 1, the FP can be used to diagnose pre-frailty and frailty [2], which are associated with adverse outcomes in CKD populations [6-11]. Studies have not evaluated the change in frailty status following exercise interventions in CKD populations. However, McAdams-DeMarco et al demonstrated an improvement in Frailty Phenotype score of 0.3 points following transplantation [45].

3. Activities of Daily Living

The Barthel Index evaluates independence with 10 activities of daily living to generate a score between 0 and 100 [46]. Higher scores indicate greater independence.

4. Falls

The Falls Efficacy Scale-International (FES-I) tool will be used to assess fall concern [47,48]. It is a self-report questionnaire that asks individuals to rate their fall concern for 16 situations on a four-point scale. The answers are totalled to provide a cumulative score between 16 and 64. A score between 16 and 19 indicates low fall concern, between 20 and 27 moderate fall

concern and between 28 and 64 high fall concern. The number of falls within the preceding 6 months will also be recorded.

5. Symptom-Burden

The Palliative Care Outcome Scale-Symptoms RENAL (POS-S RENAL) will be used to assess symptom burden [49]. The POS-S RENAL questionnaire asks individuals to report 17 symptoms that may have affected them over the preceding week and to indicate to what extent. Each symptom is scored and scores totalled to create a symptom-burden score with higher scores representing greater symptom-burden.

6. HRQOL

The Short Form-12v2 (SF-12) comprises 12 questions that are used to assess HRQOL [50,51]. The answers are used to produce an 8-scale profile of health and well-being and to generate physical and mental health summary measures. Higher SF-12 scores represent better HRQOL. The proposed minimal important difference for SF-12 summary scales is 3 T-score points [52].

Data Management

All electronic study data will be recoded on a secure, password-protected database on the LTHTR server. The server is only be accessible using password-protected user profiles on LTHTR computers. Participant names and hospital identification numbers will not be recorded on this database; participants will be identified by a study-specific participant number. There will not be a formal data monitoring committee. However, data will be managed in accordance with the LTHTR Information Governance Policy.

Analysis Plan

As recommended by the 2010 CONSORT guidelines [38], feasibility quantitative outcome measures will be reported descriptively with 95% confidence intervals. This will include the proportion of eligible patients and recruited participants, participants who adhere to the intervention, participants who complete all outcome assessments and participants lost to follow-up. Secondary outcome measures will also be reported descriptively with 95% confidence intervals. The standard deviation of walking speed will be estimated for both trial arms to inform the sample size calculation for a definitive RCT. SPSS software (version 25, IBM Corp) will be used for statistical analysis.

Qualitative data will be analysed using thematic analysis whereby narrative segments will first be coded and then translated into more abstract themes in an iterative manner [53]. NVivo software (version 12.5.0, QSR International) will be used to support analysis. Two members of the researcher team will compare themes to ensure all codes are represented. Qualitative and quantitative findings will be linked using a triangulation approach as described by Farmer et al [54] to provide a more comprehensive understanding of trial and intervention acceptability.

Adverse Events

Serious adverse events are defined as any episode during the study period that requires inpatient hospitalisation, results in persistent/significant disability, is life threatening or results in death. All adverse events will be discussed with the medically-trained Chief Investigator who will assess seriousness and causality. All adverse events will be reported to the study sponsor and all suspected unexpected serious adverse reactions reported to the

regional ethics committee. The trial will be stopped prematurely if three or more suspected unexpected serious adverse reactions occur.

Study Steering Committee

A study steering committee will provide scientific, ethical and financial oversight of research activity. The committee comprises clinicians, physiotherapists, academics, a study sponsor representative and a patient representative. Meetings will be held during before, during and on completion of the study. The patient representative will be remunerated as recommended by INVOLVE.

Ethics and Dissemination

Study ethical approval has been granted by the North West Greater Manchester East Research Ethics Committee (reference 18/NW/0211) and the National Health Service (NHS) Health Research Authority (project reference 244772). The LTHTR Centre for Health Research and Innovation accepted the role and responsibilities of study sponsorship. The study is subject to the LTHTR Internal Research and NIHR audit programmes to ensure all research activities are performed in accordance with the international standards of Good Clinical Practice, United Kingdom clinical trials legislation and trust policies. The trial is registered with the International Standard Randomised Controlled Trial Number Registry (ISRCTN87708989). Protocol amendments approved by the Research Ethics Committee/NHS Health Research Authority will be communicated with the study sponsor, study team and, where necessary, the trial registry.

The study dataset will not be made publicly available as it may be possible to identify participants from interview transcripts and as this pilot study does not aim to use quantitative data to demonstrate intervention effectiveness. The study team aim to publish the findings in a peer-reviewed journal and present the results at national and international conferences. A summary of findings will be provided to participants, a local kidney patient charity and the funding body.

DISCUSSION

To our knowledge, the EX-FRAIL CKD trial is the first pilot RCT of a progressive home-based exercise intervention specifically designed for pre-frail and frail older adults with CKD. Given the uncertainties around recruitment rates, intervention adherence and outcome measure acceptability, it is necessary to perform a pilot study prior to proceeding with a full-scale trial. These uncertainties have been considered during study design, though amendments may be required to maximise the success of a multi-centre RCT.

This study's strengths include the use of a validated frailty screening measure [27] to assist participant recruitment and, during baseline assessment, the use of the reference standard for diagnosing physical frailty, i.e. the FP [2], to determine suitability for randomisation. This methodology will minimise the number of robust individuals approached for study consent and ensure that only pre-frail and frail participants receive the intervention, thereby strengthening any conclusions that can be made following study completion. Furthermore, the nested qualitative study will complement quantitative data analysis by exploring the acceptability of the randomisation procedures, outcome measures and intervention, thus identifying areas for adaptation in a definitive RCT. An acknowledged limitation is that semi-structured interviews will be completed by a researcher involved in delivery of the study intervention, which may influence participant responses. However, the participants will be encouraged to give honest responses by reinforcing that the study objectives include to explore the acceptability of the study and identify areas requiring adaptation for a definitive RCT. For pragmatic reasons, patients that decline to participate in the study will not be invited to participate in an interview. However, participants that decide to stop exercising earlier than planned will be invited to participate in an interview to explore their experience

of the study. Furthermore, participants' rationale and motivation for enrolling in the study will be explored during interviews.

Home-based exercise programmes have been performed safely in frail older adults [22], however, perceived safety concerns (e.g. fall concerns) may influence participant adherence to the exercise programme. Participants randomised to the intervention arm will receive exercise education from a physiotherapist experienced in exercise prescription. Moreover, the exercise programme will be delivered in a graded and progressive manner with the use of weekly telephone calls that ensure safe exercise practices, explore participant uncertainties and provide ongoing support. We hope that the above will minimise participant concerns, therefore maximising participant adherence to the exercise programme.

The EX-FRAIL CKD trial aims to inform the design of a definitive multi-centre RCT that explores the benefits of a progressive, multi-component home-based exercise programme. If a definitive RCT demonstrates improvements in the physical function of participants, associated improvements in mobility, fall concern, independence, symptom-burden and HRQOL are anticipated, supporting the case for a home-based exercise programme within routine clinical care.

Trial Status

The study opened in August 2018 and the first participant was recruited in November 2018. Data collection was completed in December 2019.

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TABLES

Table 1. The Frailty Phenotype.

Frailty Phenotype Component	Measure
Unintentional Weight Loss	≥10 pounds or ≥5% body weight over the preceding 12 months.
Weakness	Hand grip strength will be assessed in the seated position with the elbow positioned at 90 degrees, supported by the arm of a chair, and with a hand-grip dynamometer (Takei 5101 GRIP-A dynamometer, Takei Scientific Inst. Co. Ltd., Niigata, Japan) supported by the assessor. Both arms will be examined with the highest score from three efforts from each side used for analysis. The body mass index and gender stratified hand grip strength cut-offs proposed by Fried et al are used to define weakness [2].
Slowness	Walking speed (15 feet) will be assessed as outlined in the section titled 'Physical Function'. The height and gender stratified walking speed cut-offs proposed by Fried et al are used to define slowness [2].
Low Physical Activity	A modified version of the Minnesota Leisure Time Questionnaire [55] will be used to assess physical activity. Low physical activity is defined as <383 kcal/wk for men and <270 kcals/wk for women [2].
Self-perceived Exhaustion	The CES-D Scale will be used to assess self-perceived exhaustion [56]. Participants will be read the following statements: (1) I felt that everything I did was an effort. (2) I could not get going. Participants will then be asked, 'How often in the last week did you feel this way?' and provided the following scale: 0 = rarely or none of the time, 1 = some of the time, 2 = moderate amount of the time, 3 = most of the time. Self-perceived exhaustion is defined as an answer ≥2 for either statement [2].
Frailty is diagnosed if 3 or more frailty components are present.	
Pre-frailty is diagnosed if 1 or 2 frailty components are present.	

kcal/wk, Kilocalories per week; CES-D, Center for Epidemiological Studies Depression.

Table 2. Schedule of Assessments

Assessment	Time		
	Screening	Baseline	Follow-Up
Clinical Frailty Scale	X		
Clinical Characteristics	X	X	
Weight, Height, HR, BP		X	X
Laboratory Variables	X	X	
Frailty Phenotype		X	X
SPPB		X	X
Barthel Index		X	X
SF-12		X	X
FES-I		X	X
POS-S RENAL		X	X
Semi-structured Interview			X

HR, Heart Rate; BP, Blood Pressure; SPPB, Short Physical Performance Battery; SF-12, Short Form-12v2; FES-I, Falls Efficacy Scale-International; POS-S RENAL, Palliative Care Outcome Scale-Symptoms RENAL.

Table 3. The EX-FRAIL CKD Exercise Programme.

Exercise	Level 1	Level 2	Level 3	Level 4
1. Walking	Walk for 1 minute	Walk for 2 minutes	Walk for 10 minutes	Walk for 15 minutes
2. Lower leg extension	Seated leg extension*	Seated leg raise*	Seated weighted (0.5kg) leg raise*	Seated weighted (1kg) leg raise*
3. Bilateral calf raises	Seated calf raises*	Standing calf raises placing hands on secure surface*	Standing calf raises placing finger tips on secure surface*	Standing calf raises*
4. Sit to stand	Sit to stand using arms to assist*	Sit to stand without using arms to assist*	Sit to stand holding 0.5kg weights*	Sit to stand holding 1kg weights*
5. Wall/table push up	Wall push up**	Wall push up*	Table push up**	Table push up*
6. Marching	Marching whilst seated*	Marching whilst standing with hands on secure surface*	Marching whilst standing*	Stair step*

*3 sets of 10 repetitions; **3 sets of 5 repetitions.

Table 4. TIDier Checklist.

Item		
1.	**Brief name**	The EX-FRAIL CKD Exercise Programme
2.	**Rationale**	Described in 'Introduction' and section titled 'Intervention Development'
3.	**Materials**	Exercise guidebook, exercise diary and wrist/ankle weights.
4.	**Procedures**	Described in section titled 'Intervention Description' and 'Participant Timeline'.
5.	**Provider**	Exercise programme education will be delivered by a physiotherapist experienced in exercise prescription. Weekly telephone calls will be performed by the physiotherapist or specialist trainee with relevant experience.
6.	**Modes of delivery**	Face-to-face exercise education session followed by weekly telephone calls.
7.	**Location**	Exercise education sessions will be delivered in a private room at NIHR Lancashire Clinical Research Facility. All exercise sessions will be completed in the participant's own home.
8.	**Frequency and duration**	All participants will have an exercise education session lasting approximately 60 minutes. Participants will aim to perform three exercise sessions at home per week, lasting approximately 30-45 minutes each.
9.	**Tailoring**	Initial exercise level will be determined by frailty status, unless the physiotherapist determines otherwise due to safety concerns. An alternative exercise will be provided if a participant is unable to perform a specific exercise as originally intended.
10.	**Modifications**	Cannot be described until study completion.
11.	**Adherence and fidelity: planned**	Exercises will be delivered as described in the exercise guidebook. If modification is needed, the participant (and study team) will be provided additional documentation. Adherence will be assessed during telephone calls and review of the participant's exercise diary. Outcomes of telephone calls will be discussed to maintain fidelity.
12.	**Adherence and fidelity: actual**	Cannot be described until study completion.

NIHR, National Institute of Health Research.

Table 5. Progression Criteria.

Progression Criteria	Stop/Go Thresholds
Eligibility	**STOP:** <5% of patients eligible **GO:** >10% of patients eligible
Recruitment	**STOP:** <10% of eligible patients recruited **GO:** >30% of eligible patients recruited
Exercise Adherence **(defined as ≥2 sessions/week)**	**STOP:** <30% adherence **GO:** >70% adherence
Outcome Measure Completion **(not including lost to follow up)**	**STOP:** <70% outcome measure completion **GO:** >80% outcome measure completion
Lost to Follow-Up **(including withdrawn and lost)**	**STOP:** >50% lost to follow-up **GO:** <25% lost to follow-up

FIGURE LEGENDS

Figure 1. Study Flow Diagram.

Figure 2. Exercise Intervention Logic Model.

AUTHORS CONTRIBUTIONS

All authors contributed to the research idea and study design. ACN, TMB, HJG, and HMLY were involved in the development of the EX-FRAIL CKD exercise programme. ACN and HMLY developed the study progression criteria. ACN, TMB and HMLY contributed to the quantitative analysis plan. HMLY and KWF contributed to the qualitative analysis plan. MEB, NP, APD and SM were involved in supervision/mentorship. ACN drafted the manuscript. Each author contributed important intellectual content during manuscript revision and accepts responsibility for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

FUNDING STATEMENT

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COMPETING INTERESTS STATEMENT

Unrelated to this body of work, APD has received lecture fees from speaking at the invitation of MSD and received travel support from Pharmacosmos.

LICENCE STATEMENT

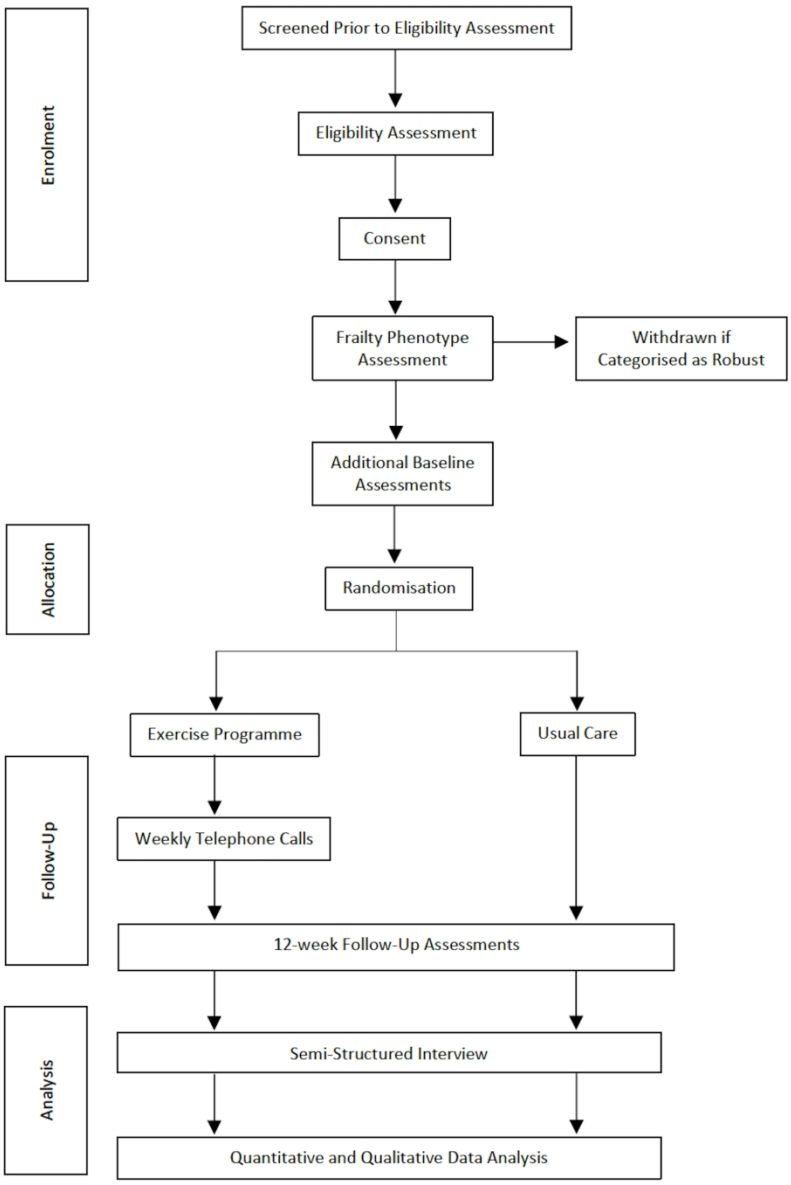

Figure 1. Study Flow Diagram.

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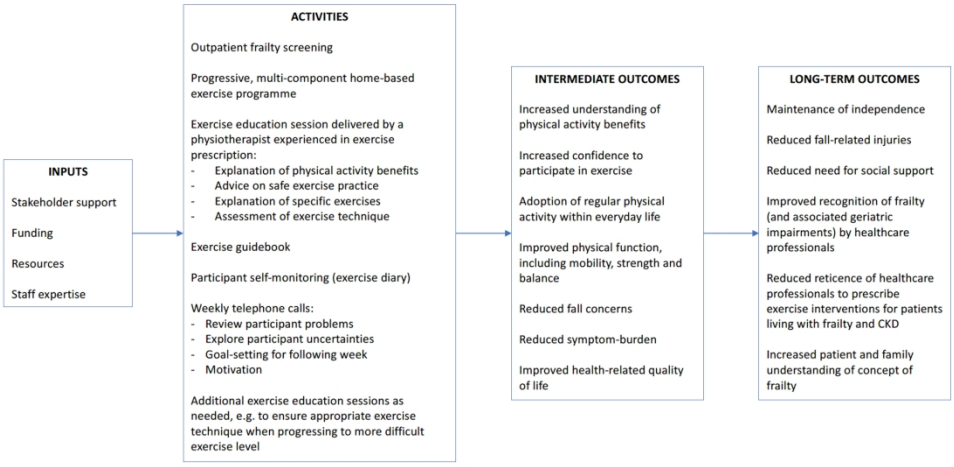

Figure 2. Exercise Intervention Logic Model.

316x153mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1,5
	2b	All items from the World Health Organization Trial Registration Data Set	7-25
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	39,40
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	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	39,40
	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)	22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9, 13-14
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
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	10
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)	11,12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-16
	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)	14-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	17-20
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)	11-12

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	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11,12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-20
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12, 17-20

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21-22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
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)	22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11,12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	39,40
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	
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	
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	23
	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	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
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	

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