BMJ Open

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046945
Article Type:	Protocol
Date Submitted by the Author:	13-Nov-2020
Complete List of Authors:	Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences Wilkinson, Thomas ; University of Leicester, Department of Health Sciences Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Brady, Emer; University of Leicester, Department of Cardiovascular Sciences Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology Cooper, Nicola; University of Leicester, Department of Health Sciences Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Smith, Alice; University of Leicester, Department of Health Sciences Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit

Keywords:	Renal transplantation < NEPHROLOGY, CARDIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Roseanne E Billany[1,2], Noemi Vadaszy[3], Nicolette C Bishop[4], Thomas J Wilkinson[3], Sherna Adenwalla[1,2], Katherine A Robinson[1], Kathryn Croker[2], Emer M Brady[1], Joanne Wormleighton[5], Kelly Parke[1,5], Nicola J Cooper[3], Angela C Webster[6], Jonathan Barratt[1,2], Gerry P McCann[1], James O Burton[1,2,5], Alice C Smith[3], Matthew PM Graham-Brown[1,2]

[1] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[2] John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK
[3] Department of Health Sciences, University of Leicester, Leicester, UK
[4] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK
[5] Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK
[6] Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and Transplant Research, Westmead Hospital, Sydney, NSW, Australia.

Corresponding author:
Dr Matthew Graham-Brown
Department of Cardiovascular Sciences
University of Leicester
Leicester
United Kingdom
mgb23@leicester.ac.uk

Keywords: kidney transplantation, home-based exercise, cardiovascular disease, feasibility, cardiac MRI

Abstract: 300
Word count: 4402

ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population, evidence is limited, and physical activity levels and patient activation towards exercise and self-management are low. This pilot study will assess the feasibility of delivering a structured, home-based exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise program.

Methods and analysis: Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-based combined resistance and aerobic exercise intervention or; (2) the control; usual care. Intervention participants will have one introductory session for instruction and practice of the recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access to instructional videos. Outcomes, to be assessed prior to randomisation and post-intervention, include: cardiac structure and function with stress-perfusion cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of cardiometabolic health, quality of life, and patient activation. The study will also evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, and the intervention implementation. These data will be used to inform the power calculations for future definitive trials.

Ethics and dissemination: The protocol was reviewed and given favourable opinion by the East Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be published in peer-reviewed academic journals and will be disseminated to the patient and public community via social media, newsletter articles, and presentations at conferences.

Trial registration number: NCT04123951; prospectively registered.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Data on the effects of exercise interventions on the cardiac structural and functional aspects of CVD in this population are lacking and baseline values of multiparametric cardiac magnetic resonance imaging in KTRs are previously undefined.
- This study uses a novel home-based exercise intervention with the potential to translate into a widespread, low-resource intervention compared to in-centre, supervised interventions that are costly and labour intensive.
- As it can be difficult to ensure control groups are not influenced to change their lifestyle as a result of being part of the study; control participants will be offered the intervention after completion of the study.
- This study will provide quantitative and qualitative feasibility and pilot data to inform a definitive randomised controlled trial that will explore longer-term engendered lifestyle change in this population in response to a complex, home-based, lifestyle intervention.
- Secondary outcome analysis will identify the putative cardiometabolic and muscular effects of the intervention, although these results would need confirming in adequately powered studies due to the small sample size of this pilot study.

BACKGROUND

Kidney transplantation is the preferred modality of renal replacement therapy for patients with end stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage over remaining on dialysis, cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and graft loss.[1-3] Since 2015, mortality rates attributed to CVD have been rising.[3] Cardiovascular disease in kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,[2 4 5] which drive classical atheromatous coronary artery disease, and non-traditional risk factors which drive pathological changes in cardiovascular structure and function that associate with mortality.[6] Immunosuppressive agents are well known to drive traditional CVD risk factors,[2] but also drive non-traditional cardiometabolic risk factors.[7 8] Non-traditional cardiometabolic risk factors, including endothelial dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-mineral metabolism,[9-11] are of at least equal importance in the pathogenesis of CVD in KTRs.[6] This is further illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate cardiovascular risk in patients with chronic kidney disease (CKD);[10] coronary revascularisation does not improve outcomes for KTRs as it does in the general population[11] and cardiac events are more likely to be fatal in KTRs.[12]

Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”, is characterised by stereotypical changes in the cardiovascular structure and function of the heart such as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,[13] myocardial fibrosis,[14] and aortic stiffness[15]; all of which relate to poor cardiovascular outcomes.[16 17] Although structural and functional improvements of the heart and vessels have been seen post-transplantation in some studies,[18] others have shown no regression[19] and parameters such as LVH are independent factors for cardiac failure and mortality in KTRs.[20] Cardiac magnetic resonance imaging (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic function to be reproducible in patients with kidney disease,[21-23] making CMR the ideal imaging modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.

Numerous epidemiological studies have observed the association between low levels of physical activity and increased prevalence of CVD risk factors,[24-26] and an inverse relationship between physical activity and all-cause and CVD mortality.[27 28] Physical activity levels in KTRs are lower than the general population,[29 30] with only 27% classified as meeting national recommended physical activity levels.[31] Whilst physical activity levels improve in the year following transplantation, they plateau after one-year.[30] In the general population, lifestyle changes that increase physical activity through structured exercise lower mortality.[32 33] Despite this evidence, there is a lack of rigorous research into the role of

increased physical activity in mitigating cardiovascular risk in KTRs.[34] Recent consensus recommendations from experts and stakeholders highlighted the need for a priority research agenda in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this patient population.[35] Whilst supervised exercise interventions in KTRs improve cardiorespiratory fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic profile,[36-38] vascular stiffening,[37] weight,[39] and inflammation,[40] they are not realistically deliverable in the current financial climate and have not translated to clinical practice. Furthermore, exercise habits following in-centre supervised programs are not maintained[41-43] which can be potentially attributed to low levels of patient activation (a measure of a person's skills, confidence, and knowledge to manage their own health) and a failure for such programs to engender sustained lifestyle changes.[44] [45] Home-based exercise training programs have been shown to be deliverable in patients on dialysis and patients undergoing cardiac rehabilitation,[46] [47] but the effectiveness and deliverability of home-based exercise interventions are untested in KTRs. It cannot be assumed that such programs will be acceptable to KTRs, whose home-lives, social and occupational circumstances are significantly different to dialysis and cardiac patients. Many KTRs have had enforced sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes at work may be different.

Objectives

The aims of this study are to evaluate the impact of a 12-week, home-based exercise intervention in KTRs with increased cardiometabolic risk, specifically addressing:

1. The deliverability and feasibility of the home-based exercise intervention in KTRs, defining recruitment, retention, and compliance;
2. Potential cardiovascular structural and functional parameters measured using stress-perfusion CMR;
3. Cardiorespiratory fitness and strength;
4. Biochemical markers of cardiometabolic health, body composition, physical function, and quality of life;
5. Patient activation and continued adherence to the prescribed home-based exercise program.

Two sub-studies will assess:

1. The acceptability of the intervention through qualitative semi-structured interviews post-intervention.
2. The differences between cardiorespiratory fitness in 'healthy controls' versus KTRs.

METHODS AND ANALYSIS

ECSERT trial design

This study is a prospective, randomised, open-label, blinded endpoint (PROBE) pilot study. The study flowchart is presented in Figure 1.

Participant identification and recruitment

Fifty KTRs with a stable kidney transplant of >1 year will be recruited from University Hospitals of Leicester NHS Trust (UHL) kidney transplant outpatient clinic lists. There are approximately 400-420 KTRs registered in UHL kidney transplant outpatient clinics. Full lists of inclusion and exclusion criteria are included in Table 1. Patients will be screened by a clinician for eligibility to enter the study. Eligible patients will be approached (via telephone, post, or during their routine clinical appointment) and will be provided with verbal and written study information and time to consider without further contact (at least 24 h). Additionally, eligible patients who have given prior consent to be contacted regarding research opportunities will be contacted via post. All patients will be given the opportunity to discuss the study in more detail and to consider their participation. Consent will be performed by the Chief Investigator (MBG) according to the rules of good clinical practice.

Randomisation

Following baseline assessment, participants will be randomly allocated (1:1) to either; (1) a 12-week home-based combined resistance and aerobic exercise intervention (n=25) or; (2) control (n=25; receiving usual care). Randomisation will be blocked (using computer-generated random permuted blocks with allocation concealment; https://www.sealedenvelope.com/simple-randomiser/v1/) to ensure periodic balancing. The Clinical Trials Facilitator will perform the randomisation. Given the nature of the intervention, it is not possible for the participants to be blinded to their allocation.

Intervention and comparator arms

Intervention Group: 12-week home-based combined aerobic and resistance training

The 12-week, home-based, structured exercise program includes aerobic and resistance training (4-5 sessions in total per week). Participants will be advised to complete a warm-up and cool-down prior to and following each session, respectively. Participants will continue to receive usual clinical care.

Aerobic component

The aerobic component of the intervention will be walking, jogging, cycling, or similar, depending on resources available and participant preference. Participants will be asked to complete 2-3 sessions per week using a rating of perceived of exertion (RPE)[48] of 13-15 (somewhat hard) for 20-30 min. RPE will

be collected throughout cardiopulmonary exercise tests (CPET) and participants will be educated on its use during the instructional session(s).

Resistance component

The resistance component of the exercise intervention will include a combination of 6-8 exercises per session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row, reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has modifications for different abilities and may be pragmatically adjusted or changed throughout the study as required. These exercises were chosen based on their ability to be modified, their subjective difficulty, and their safety when being performed by participants new to exercise in an unsupervised environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of 10 repetitions (at 60% 1 repetition maximum (RM)), gradually increasing to 3-6 sets of 10 repetitions over the study period with a minimum of 30 sec rest between sets. These figures may be adjusted to accommodate different abilities and different rates of progression.

Participants will be provided with an exercise diary which includes additional instructions, dumbbells and resistance bands, and access to educational and instructional videos. Instructional videos will include: the importance of an active and healthy lifestyle, the importance of warming up and cooling down and how to do it, a reminder of how to use the RPE scale, demonstrations of each resistance exercise, and information about the aerobic component (videos can be viewed here: https://www.youtube.com/playlist?list=PLwbE3AF9Ej_Vul5uoiF-C9Cl8wrgKz5Nv). Participants will receive a telephone call from a member of the research team every two weeks in order to discuss progression of the exercise and address any issues that may arise.

Control group: 'Usual care'

Participants in the control group will be asked to maintain their current lifestyle and exercise habits throughout the study. This includes continuing to attend any scheduled clinic appointments and taking prescribed medication as normal. As part of routine care, KTRs are recommended to take regular exercise and maintain a healthy lifestyle. This advice will be reiterated to patients in the control group to ensure the intervention is being appropriately compared to best-practice standard care. Participants will be asked to complete a 'control diary' to note any exercise, medication changes, illness, and other relevant information. Once control participants complete the post-intervention

assessments, they will be offered the opportunity to complete the same intervention as the exercise group.

Study timeline

Baseline assessments

The ECSERT study timeline is shown in Figure 1. Baseline assessments will be carried out on the same day and in conjunction with routine clinical appointments to prevent additional travel.

Collection of routine clinical information and cost-effectiveness

Clinical information will be extracted from the medical notes including: age, gender, ethnicity, primary cause of kidney failure, transplant type, transplant vintage, dialysis duration, comorbidities, blood/urine results, current medication, and smoking habits. This information will be used to primarily capture cofounding variables and during analyses of differences and similarities between groups.

A questionnaire will be administered at baseline to capture the previous 3 months of self-reported healthcare utilisation including: inpatient and outpatient appointments, emergency care, community and primary care services, support services, and changes in medications. This will be compared to data gathered from healthcare records allowing validation of the questionnaire for future cost-effectiveness analyses.

Cardiac stress MRI

All participants will undergo a comprehensive adenosine-stress perfusion CMR scans at baseline and on study-completion. Participants will be scanned on a 3T platform (Skyra, Siemens Medical Imaging, Erlangen, Germany) with an 18-channel phased-array receiver coil. New-generation gadolinium-based contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m^2 will be given for perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m^2 will undergo non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

- Left and right-ventricular structure and function (left ventricular mass, left and right ventricular volumes and ejection fractions);[49]
- Tissue-characterisation with native and post-contrast T1 mapping and delayed gadolinium enhancement;[50-52]
- Myocardial systolic-strain and peak early-diastolic strain rate;[23]
- Quantitative perfusion imaging (coronary blood-flow to quantify coronary reserve and ischaemia);[53]
- Aortic distensibility.[21]

Quadriceps MRI

At the end of the CMR scan, participants will immediately undergo an MRI scan of the quadriceps muscle in their right leg to assess muscle size and muscle quality as previously described.[54]

Cardiopulmonary exercise test

A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W) every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min[55]. Participants will be encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured ($\dot{V}O_2$peak) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true maximal (plateau) $\dot{V}O_2$ ($\dot{V}O_2$max) is less commonly achieved in deconditioned and/or clinical patients. The test will be in the presence of a cardiac nurse to confirm safety to commence exercise training. A non-invasive monitor (Moxy, Fortiori Design LLC., Minnesota, USA) will be worn on the quadriceps muscle which uses near infrared spectroscopy (NIRS) to measure local oxygen saturation (SmO_2) and total haemoglobin (THb) of the muscle.

Lower limb Strength and muscular endurance

Isometric and isokinetic muscle (knee extension) strength, of the dominant leg, will be assessed using a dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA). Peak isometric strength (torque, Nm) will be assessed from three repetitions of maximum effort at 90º knee flexion for ~3-5 sec with 60 sec rest. Isokinetic strength will be assessed at three speeds for one set of five repetitions at each speed: 60°/sec, 90°/sec, and 120°/sec. Participants will perform a 'sit-to-stand-60' (STS-60) test measuring how many sit-to-stand cycles can be performed over 60 sec.

Handgrip strength

Peak grip strength of the left and right hands will be assessed with a hand dynamometer (Jamar Plus+; Sammons Preston, Bolingbrook, IL). Each hand will be alternatively tested for three attempts each and the highest value on each hand with be recorded.

Gait speed

A 4 m walk test will be used to assess gait speed. Participants will be asked to walk 4 m at their 'usual walking pace' for one practice and two, timed trials. The average score (m/sec) of the timed trials will be recorded.

Functional mobility

The 'timed-up-and-go' test (TUAG) will be used to assess functional mobility.[56 57] The participant is timed whilst rising from the seated position on a chair, walking 3m, turning around, and returning to a seated position.

Balance and postural stability

Postural stability and balance will be assessed using a previously reported method[58] with a FysioMeter device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to software on a portable computer (FysioMeter ApS, Brønderslev, Denmark).

Quadriceps ultrasound and myotonometry

Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D ultrasonography (Clarius C3 HD Scanner, Clarius, Burnaby BC, Canada; 6 MHz) under resting conditions with the participant lying prone at a 45° as previously described.[54] Rectus femoris and vastus lateralis thickness, subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of the viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

Anthropometric measures

Anthropometric measures of height, body mass, and waist and hip circumference will be attained in accordance with standard protocols.[59] Bioelectrical impedance analysis (BIA) performed on an InBody analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat percentage, fat-free mass) and is validated for use in patients with CKD.[60 61]

Survey pack

Participants will be provided with a survey pack containing the following questionnaires:

(1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the presence and severity of disease related symptoms. The I-POS-Renal was developed based on the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms common in CKD such as pruritus and restless legs.[62]

(2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess generic health outcomes from the patient's perspective.[63]

(3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert scale that covers physical fatigue, functional fatigue, emotional fatigue, and social consequences of fatigue with excellent internal consistency and test-retest reliability.[64 65]

(4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval.[66]

(5) Patient Activation Measure (PAM): a validated, licenced tool that has been extensively tested with reviewed findings from a large number of studies. It measures the spectrum of

knowledge, skills, and confidence in patients and captures the extent to which they feel engaged and confident in taking care of their condition ('activation').[67]

(6) Brief Health Literacy Screen (BHLS): a 3-item questionnaire to identify inadequate health literacy,[68] validated against longer screening tools in populations with ESKD.[69,70]

(7) The Global Physical Activity Questionnaire (GPAQ): developed by the World Health Organisation (WHO) for physical activity surveillance in countries. It collects information on physical activity participation in three settings or domains (activity at work, travel to and from places, and recreational activities) as well as sedentary behaviour, comprising 16 questions.[71]

(8) Duke Activity Status Index (DASI): a 12-item questionnaire that uses self-reported physical work capacity to estimate peak metabolic equivalents and has been shown to be a valid measurement of functional capacity.[72]

Habitual physical activity

Objective data on habitual physical activity levels over a 7-day period (ideal minimum 6-days)[73] will be gained from tri-axial accelerometers (GENEActiv, ActivInsights Ltd., Cambridge, UK).

Blood and urine sampling

Venous blood (30 ml) will be collected using venepuncture of the antecubital vein and prepared and stored appropriately for the following analysis:

- Circulating markers of cardiovascular disease
- Circulating markers of systemic inflammation and oxidative stress
- Blood glucose and HbA1c
- Lipids and triglycerides
- Full blood count and renal profile

A urine sample will be requested to ascertain urinary protein:creatinine ratio.

Follow-up assessments

Follow up visits are summarised in Figure 1. An instructional session (or more if required) following baseline assessments will allow the intervention group to become familiar with the exercise requirements and allow the research team to ensure safety and competence before commencing the 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-week period for the intervention group only, participants will be invited to review exercise progression (via video call or in-person), particularly if participants are struggling to undertake the requisite amount of exercise, and as a refresher of the intervention. This combined with regular contact from research staff should aid participant compliance and monitoring.

Final assessments will be conducted for the exercise and control groups within 7 days of completing the 12-week exercise or control period. Assessments completed will be identical to the baseline visit with the addition of a 'patient satisfaction questionnaire' to allow pragmatic development of the study. This will also be offered to participants who withdraw from the trial. Three months after completing the exercise intervention, participants will be contacted for a semi-structured one-to-one telephone interview. This will aim to understand the impact of the intervention, if any, on subsequent lifestyle and exercise habits.

Sub-studies

Additional informed consent will be sought for:

1. Ten 'healthy' control participants to undertake a CPET to assess the differences, if any, between CPET parameters in 'healthy controls' versus KTRs, particularly during the recovery period.
2. KTRs completing the exercise intervention will be invited to undertake a semi-structured interview (via telephone, video call, or in-person) incorporating exercise self-efficacy, enjoyment, difficulties encountered, perceived advantages and disadvantages of the intervention, and study design. Participants who withdraw before the end of the intervention will also be invited to attend, although in line with ethical standards, this will be optional.

Sample size

The purpose of this pilot study is to obtain appropriate data to adequately power future definitive trials;[74] a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on accepted values to provide adequate estimates of standard deviations for future power calculations.[75]

Data collection and management

Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will be entered into a secure database and will only be accessible on password-protected computers at UHL and University of Leicester by relevant members of the study team. No identifying information will be kept in electronic form. All source data and original participant identities will be kept in a locked office in the trial site file only at UHL.

Data analysis

Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous data to be expressed as mean (± standard deviation), if normally distributed or median (interquartile range) if not. To investigate the differences between interventions we will use analysis of (co-) variance. Independent samples t-tests and Mann-Whitney U tests will be used assess for baseline

differences between variables for normally and non-normally distributed data respectively. These data will be used to inform the power calculation for future definitive trials.

Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive thematic analysis to explore themes emerging from patient journeys through, and experiences of, the interventions and outcome measures.

Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

- *Eligibility:* the percentage of patients screened who are eligible.
- *Recruitment rate:* the percentage of patients eligible who consent to the trial and the monthly recruitment rate.
- *Adherence to the exercise intervention:* the number of completed sessions per week and specific intensity and durations achieved.
- *Acceptability of randomisation:* comparison of the final group characteristics and identification of any stratification variables, if applicable.
- *Attrition rate:* the number of participants that drop-out of the study.
- *Outcome acceptability:* the percentage of missing data for each outcome measure.
- *Safety:* The number of self-reported injuries or adverse events throughout the trial.

The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility (≥50%), recruitment success of 20% of eligible participants (≥2 participants per month), adherence (an average of 3 exercise sessions per week) and attrition (≤30%).

Safety reporting

All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) or serious adverse reactions (SARs) will be recorded from the time a patient enters the study to the final study visit. Each AE or AR will be considered for severity, causality, and expectedness and may be reclassified as an SAE or SAR if required.

An SAE is any AE that:

- is life threatening
- requires hospitalization or prolongation of a hospital admission
- results in a persistent or significant disability/incapacity
- is a congenital anomaly
- results in death

All AEs and ARs will be documented in participants CRFs, medical notes, and an AE log and will record the following information: description, date of onset and end date, severity, assessment of

relatedness to study, other suspect device and action taken. Only AEs that are judged to be related to the study intervention or procedures will be reported to the sponsor.

All SAEs will be reported by the investigators to the sponsor within 24 hours of discovery or notification and the report will be signed by the chief investigator within 7 days. If the SAE is deemed related to the research procedures or intervention and is unexpected, a report will be sent to the research ethics committee (REC) within 15 days.

Patient and public involvement

A patient and public involvement (PPI) group has been convened and will meet with the research team to review progress and address issues that arise throughout the duration of the study. The PPI partners will assist in the interpretation and dissemination of results. The trial was designed in consultation with PPI partners who advised on intervention content and outcome measure acceptability, paying particular attention to patient burden, ensuring outcome measures would not over-burden participants. The PPI group approved the final design and duration of this intervention and advised the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise capability.

Changes to the study protocol following the COVID-19 pandemic

The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst patient safety remains the absolute priority of clinical and research teams, there is a need for research to continue in a safe way that balances the benefits of continuing programs of research against the risks from COVID-19. We have amended the study protocol in several ways to reduce any additional exposure of patients to clinical environments where COVID-19 may be present:

- We have reduced the number of study visits to a minimum. The original study flow diagram is included in Additional file 1. All interim assessments have been removed in the modified protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient clinical care. That is to say, when they attend for their baseline and follow-up study visits they will have their clinical review and clinical blood tests as they would for their normal clinical care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical environment over-and-above their normal care.
- The original study design included a 2-week face-to-face training period where participants would attend the hospital to learn how to complete the exercises and the exercise program with a member of the research team. This training period will now be done remotely, via video conferencing, with discussion and feedback over the telephone and using the instructional videos and literature that support the home-based exercise intervention.

- When participants attend for their study visits, departmental procedures have been updated to now include meticulous cleaning of all equipment before and after use, one-way flows of participants to ensure participants do not mix, and the use of personal protective equipment for all staff and participants.

The above changes have been agreed with the local REC and the study sponsor and have allowed recommencement of study recruitment and procedures.

DISCUSSION

This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR to evaluate the structural and functional changes of the heart in this at risk population.

Qualitative data will provide valuable personal perspectives on the acceptability of this specific exercise program. Transplant recipients experience complex medical journeys and are likely to have specific unmet needs in the area of exercise and lifestyle. This will be valuable information for future randomised controlled trials (RCTs) and exercise guideline development.

Home-based intervention outcomes are reliant on accurate reporting by participants with regards to frequency, intensity, and duration of exercise performed. This is often a limitation of unsupervised interventions. We will ensure participants are correctly advised of how to monitor and report their exercise completion throughout the trial and encourage this through telephone communications.

We anticipate that a positive outcome will lead to both an increased understanding of the specific exercise requirements of KTRs and the development of new programs that promote longer-term engendered lifestyle change that can be incorporated into standard practice with much lower financial implications than in-centre supervised rehabilitation.

DECLARATIONS

Ethical issues

University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). This manuscript is quorate with the most recent approved protocol (version 5 01.05.2020). Relevant parties will be informed of any substantial protocol modifications. Steps have been taken when designing this protocol to minimise the ethical implications and ensure patient welfare. The study will comply with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research Governance Framework for Health and Social Care.

Twitter: REB, @RBillany; MGB, @DrMattGB.

Author contributions: MGB is the chief investigator for this trial. REB and MGB wrote this manuscript. All authors contributed to the development of the study design and protocol lead by MGB. All authors reviewed and approved the final version of this manuscript.

Funding: This study is funded by a project grant from Kidney Research UK (ref: KS_RP_003_20180913). Neither the sponsor nor the funder had or will have any input into study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Acknowledgements: This research is supported by the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests: None declared.

Availability of data: On completion the results of this study will be published in peer-reviewed journals and presented at national and international conferences. Contributions of all authors to manuscripts arising from this study will be made explicit in the relevant of each individual journal. Participant level data will be available following publication of results on request to the Chief Investigator. Results will also be disseminated to the patient and public community via social media and newsletter articles and presentations at patient conferences and forums, led by the patient partners. It is anticipated that the results of this study will inform future design of larger RCTs in this subject area and contribute to future specific physical activity guidelines in this population.

Consent for publication: Not applicable.

REFERENCES

1. Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. *Nephron* 2016;132 Suppl 1:111-44. doi: 10.1159/000444819 [published Online First: 2016/04/27]
2. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. *World J Transplant* 2015;5(4):183-95. doi: 10.5500/wjt.v5.i4.183
3. UK Renal Registry. UK Renal Registry 21st Annual Report – data to 31/12/2017. Bristol, UK, 2019.
4. Kasiske BL, Guijarro C, Massy ZA, et al. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996;7(1):158-65. [published Online First: 1996/01/01]
5. Carpenter MA, John A, Weir MR, et al. BP, cardiovascular disease, and death in the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *J Am Soc Nephrol* 2014;25(7):1554-62. doi: 10.1681/asn.2013040435 [published Online First: 2014/03/15]
6. Mall G, Huther W, Schneider J, et al. Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrol Dial Transplant* 1990;5(1):39-44. doi: 10.1093/ndt/5.1.39 [published Online First: 1990/01/01]
7. Bakri RS, Afzali B, Covic A, et al. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. *Clin Transpl* 2004;18(2):201-04. doi: 10.1111/j.1399-0012.2004.00156.x
8. Liefeldt L, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transplant International* 2010;23(12):1191-204. doi: 10.1111/j.1432-2277.2010.01159.x
9. Van Laecke S, Malfait T, Schepers E, et al. Cardiovascular disease after transplantation: an emerging role of the immune system. *Transpl Int* 2018;31(7):689-99. doi: 10.1111/tri.13160 [published Online First: 2018/04/04]
10. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 2007;50(3):217-24. doi: 10.1016/j.jacc.2007.03.037 [published Online First: 2007/07/17]
11. Aalten J, Peeters SA, van der Vlugt MJ, et al. Is standardized cardiac assessment of asymptomatic high-risk renal transplant candidates beneficial? *Nephrol Dial Transplant* 2011;26(9):3006-12. doi: 10.1093/ndt/gfq822 [published Online First: 2011/02/16]
12. Kasiske BL. Epidemiology of cardiovascular disease after renal transplantation. *Transplantation* 2001;72(6 Suppl):S5-8. doi: 10.1097/00007890-200109271-00003 [published Online First: 2001/10/05]
13. de Albuquerque Suassuna P, Sanders-Pinheiro H, de Paula R. Uremic Cardiomyopathy: A New Piece in the Chronic Kidney Disease-Mineral and Bone Disorder Puzzle. *Front Med (Lausanne)* 2018;5:206-06. doi: 10.3389/fmed.2018.00206
14. Aoki J, Ikari Y, Nakajima H, et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 2005;67(1):333-40. doi: 10.1111/j.1523-1755.2005.00086.x [published Online First: 2004/12/22]
15. Mark PB, Doyle A, Blyth KG, et al. Vascular function assessed with cardiovascular magnetic resonance predicts survival in patients with advanced chronic kidney disease. *J Cardiovasc Magn Reson* 2008;10:39. doi: 10.1186/1532-429x-10-39 [published Online First: 2008/08/19]
16. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47(1):186-92. doi: 10.1038/ki.1995.22 [published Online First: 1995/01/01]
17. Foley RN, Parfrey PS, Harnett JD, et al. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995;5(12):2024-31. [published Online First: 1995/06/01]

18. Ali A, Macphee I, Kaski JC, et al. Cardiac and vascular changes with kidney transplantation. *Indian J Nephrol* 2016;26(1):1-9. doi: 10.4103/0971-4065.165003
19. Patel RK, Mark PB, Johnston N, et al. Renal Transplantation Is Not Associated with Regression of Left Ventricular Hypertrophy: A Magnetic Resonance Study. *Clin J Am Soc Nephrol* 2008;3(6):1807-11. doi: 10.2215/cjn.01400308
20. Devine PA, Courtney AE, Maxwell AP. Cardiovascular risk in renal transplant recipients. *J Nephrol* 2019;32(3):389-99. doi: 10.1007/s40620-018-0549-4 [published Online First: 2018/11/07]
21. Graham-Brown MPM, Adenwalla SF, Lai FY, et al. The reproducibility of cardiac magnetic resonance imaging measures of aortic stiffness and their relationship to cardiac structure in prevalent haemodialysis patients. *Clin Kidney J* 2018;11(6):864-73. doi: 10.1093/ckj/sfy042
22. Graham-Brown MPM, Rutherford E, Levelt E, et al. Native T1 mapping: inter-study, inter-observer and inter-center reproducibility in hemodialysis patients. *J Cardiovasc Magn Reson* 2017;19(1) doi: 10.1186/s12968-017-0337-7
23. Graham-Brown MP, Gulsin GS, Parke K, et al. A comparison of the reproducibility of two cine-derived strain software programmes in disease states. *Eur J Radiol* 2019;113:51-58. doi: 10.1016/j.ejrad.2019.01.026 [published Online First: 2019/04/01]
24. Jebb SA, Moore MS. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc* 1999;31(11 Suppl):S534-41. doi: 10.1097/00005768-199911001-00008 [published Online First: 1999/12/11]
25. Kriska AM, Saremi A, Hanson RL, et al. Physical activity, obesity, and the incidence of type 2 diabetes in a high-risk population. *Am J Epidemiol* 2003;158(7):669-75. doi: 10.1093/aje/kwg191 [published Online First: 2003/09/26]
26. Pereira MA, Folsom AR, McGovern PG, et al. Physical activity and incident hypertension in black and white adults: the Atherosclerosis Risk in Communities Study. *Prev Med* 1999;28(3):304-12. doi: 10.1006/pmed.1998.0431 [published Online First: 1999/03/12]
27. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J* 2013;77(2):281-92. doi: 10.1253/circj.cj-13-0007 [published Online First: 2013/01/19]
28. Barengo NC, Hu G, Lakka TA, et al. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 2004;25(24):2204-11. doi: 10.1016/j.ehj.2004.10.009 [published Online First: 2004/12/14]
29. Nielens H, Lejeune TM, Lalaoui A, et al. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. *Nephrol Dial Transplant* 2001;16(1):134-40. doi: 10.1093/ndt/16.1.134 [published Online First: 2001/02/24]
30. Dontje ML, de Greef MH, Krijnen WP, et al. Longitudinal measurement of physical activity following kidney transplantation. *Clin Transplant* 2014;28(4):394-402. doi: 10.1111/ctr.12325 [published Online First: 2014/03/19]
31. Wilkinson TJ, Clarke AL, Nixon DGD, et al. Prevalence and correlates of physical activity across kidney disease stages: an observational multicentre study. *Nephrol Dial Transpl* 2019 doi: 10.1093/ndt/gfz235
32. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012;2(2):1143-211. doi: 10.1002/cphy.c110025 [published Online First: 2012/04/01]
33. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. *J Appl Physiol* 2011;111(5):1497-504. doi: 10.1152/japplphysiol.00420.2011 [published Online First: 2011/08/13]
34. Didsbury M, McGee RG, Tong A, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. *Transplantation* 2013;95(5):679-87. doi: 10.1097/TP.0b013e31827a3d3e [published Online First: 2013/02/01]

35. Mathur S, Janaudis-Ferreira T, Wickerson L, et al. Meeting Report: Consensus Recommendations for a Research Agenda in Exercise in Solid Organ Transplantation. *Am J Transplant* 2014;14(10):2235-45. doi: 10.1111/ajt.12874
36. Masajtis-Zagajewska A, Muras K, Nowicki M. Effects of a Structured Physical Activity Program on Habitual Physical Activity and Body Composition in Patients With Chronic Kidney Disease and in Kidney Transplant Recipients. *Exp Clin Transplant* 2019;17(2):155-64. doi: 10.6002/ect.2017.0305 [published Online First: 2018/05/17]
37. O'Connor EM, Koufaki P, Mercer TH, et al. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients - A pilot randomised controlled trial. *PLoS One* 2017;12(2):e0171063. doi: 10.1371/journal.pone.0171063 [published Online First: 2017/02/06]
38. Moraes Dias CJ, Anaisse Azoubel LM, Araujo Costa H, et al. Autonomic modulation analysis in active and sedentary kidney transplanted recipients. *Clin Exp Pharmacol Physiol* 2015;42(12):1239-44. doi: 10.1111/1440-1681.12481 [published Online First: 2015/08/19]
39. Roi GS, Stefoni S, Mosconi G, et al. Physical activity in solid organ transplant recipients: organizational aspects and preliminary results of the Italian project. *Transplant Proc* 2014;46(7):2345-9. doi: 10.1016/j.transproceed.2014.07.055 [published Online First: 2014/09/23]
40. Romano G, Simonella R, Falleti E, et al. Physical training effects in renal transplant recipients. *Clin Transplant* 2010;24(4):510-4. doi: 10.1111/j.1399-0012.2009.01098.x [published Online First: 2009/10/01]
41. Kinnafick FE, Thogersen-Ntoumani C, Shepherd SO, et al. In It Together: A Qualitative Evaluation of Participant Experiences of a 10-Week, Group-Based, Workplace HIIT Program for Insufficiently Active Adults. *J Sport Exerc Psychol* 2018;40(1):10-19. doi: 10.1123/jsep.2017-0306 [published Online First: 2018/03/10]
42. van Baar ME, Dekker J, Oostendorp RA, et al. Effectiveness of exercise in patients with osteoarthritis of hip or knee: nine months' follow up. *Ann Rheum Dis* 2001;60(12):1123-30. doi: 10.1136/ard.60.12.1123 [published Online First: 2001/11/16]
43. Timmons JF, Griffin C, Cogan KE, et al. Exercise Maintenance in Older Adults 1 Year After Completion of a Supervised Training Intervention. *J Am Geriatr Soc* 2020;68(1):163-69. doi: 10.1111/jgs.16209
44. Hibbard JH, Greene J. What The Evidence Shows About Patient Activation: Better Health Outcomes And Care Experiences; Fewer Data On Costs. *Health Affairs* 2013;32(2):207-14. doi: 10.1377/hlthaff.2012.1061
45. Skolasky RL, Mackenzie EJ, Wegener ST, et al. Patient activation and adherence to physical therapy in persons undergoing spine surgery. *Spine (Phila Pa 1976)* 2008;33(21):E784-E91. doi: 10.1097/BRS.0b013e31818027f1
46. Buckingham SA, Taylor RS, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart* 2016;3(2):e000463. doi: 10.1136/openhrt-2016-000463 [published Online First: 2016/10/16]
47. Baggetta R, D'Arrigo G, Torino C, et al. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: a secondary analysis of the EXCITE trial. *BMC Geriatr* 2018;18(1):248. doi: 10.1186/s12877-018-0938-5 [published Online First: 2018/10/22]
48. Borg GA. Perceived exertion: a note on "history" and methods. Med Sci Sports 1973;5(2):90-3. [published Online First: 1973/01/01]
49. Hunold P, Vogt FM, Heemann UW, et al. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI--study in dialysis patients examined before and after dialysis. *J Cardiovasc Magn Reson* 2003;5(4):553-61. doi: 10.1081/jcmr-120025230 [published Online First: 2003/12/11]

50. Graham-Brown MP, March DS, Churchward DR, et al. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016;90(4):835-44. doi: 10.1016/j.kint.2016.07.014 [published Online First: 2016/09/17]
51. Xu HY, Yang ZG, Zhang Y, et al. Prognostic value of heart failure in hemodialysis-dependent end-stage renal disease patients with myocardial fibrosis quantification by extracellular volume on cardiac magnetic resonance imaging. *BMC Cardiovasc Disord* 2020;20(1):12. doi: 10.1186/s12872-019-01313-2 [published Online First: 2020/01/12]
52. Graham-Brown MP, Singh AS, Gulsin GS, et al. Defining myocardial fibrosis in haemodialysis patients with non-contrast cardiac magnetic resonance. *BMC Cardiovasc Disord* 2018;18(1):145. doi: 10.1186/s12872-018-0885-2 [published Online First: 2018/07/15]
53. Xue H, Brown LAE, Nielles-Vallespin S, et al. Automatic in-line quantitative myocardial perfusion mapping: Processing algorithm and implementation. *Magn Reson Med* 2020;83(2):712-30. doi: 10.1002/mrm.27954 [published Online First: 2019/08/24]
54. Gould DW, Watson EL, Wilkinson TJ, et al. Ultrasound assessment of muscle mass in response to exercise training in chronic kidney disease: a comparison with MRI. *J Cachexia Sarcopenia Muscle* 2019;10(4):748-55. doi: 10.1002/jcsm.12429
55. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *American Journal of Respiratory and Critical Care Medicine* 2003;167(2):211-77. doi: 10.1164/rccm.167.2.211
56. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x [published Online First: 1991/02/01]
57. Hadjiioannou I, Wong K, Lindup H, et al. Test-restest reliability for physical function measures in patients with chronic kidney disease. *J Ren Care* 2019 doi: 10.1111/jorc.12310
58. Wilkinson TJ, Nixon DGD, Smith AC. Postural stability during standing and its association with physical and cognitive functions in non-dialysis chronic kidney disease patients. *Int J Nephrol Urol* 2019;51(8):1407-14. doi: 10.1007/s11255-019-02192-4
59. Eston RG, Reilly T. Kinanthropometry and exercise physiology laboratory manual : tests, procedures, and data. 3rd ed. Abingdon: Routledge 2009.
60. Chertow GM, Lowrie EG, Wilmore DW, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995;6(1):75-81. [published Online First: 1995/07/01]
61. Macdonald JH, Marcora SM, Jibani M, et al. Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transplant* 2006;21(12):3481-7. doi: 10.1093/ndt/gfl432 [published Online First: 2006/09/07]
62. Raj R, Ahuja K, Frandsen M, et al. Validation of the IPOS-Renal Symptom Survey in Advanced Kidney Disease: A Cross-sectional Study. *J Pain Symptom Manage* 2018;56(2):281-87. doi: 10.1016/j.jpainsymman.2018.04.006
63. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care* 1996:220-33.
64. Wang S-Y, Zang X-Y, Liu J-D, et al. Psychometric Properties of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) in Chinese Patients Receiving Maintenance Dialysis. *J Pain Symptom Manage* 2015;49(1):135-43. doi: 10.1016/j.jpainsymman.2014.04.011
65. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13(2):63-74. doi: 10.1016/s0885-3924(96)00274-6 [published Online First: 1997/02/01]
66. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4 [published Online First: 1989/05/01]

67. Hibbard JH, Stockard J, Mahoney ER, et al. Development of the Patient Activation Measure (PAM): Conceptualizing and Measuring Activation in Patients and Consumers. *Health Services Research* 2004;39(4p1):1005-26. doi: 10.1111/j.1475-6773.2004.00269.x
68. Chew LD, Bradley KA, & Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med*. 2004;36(8):588-594.
69. Cavanaugh KL, Osborn CY, Tentori F, et al. Performance of a brief survey to assess health literacy in patients receiving hemodialysis. *Clin Kidney J* 2015;8(4):462-468. doi:10.1093/ckj/sfv037
70. Dageforde LA, Cavanaugh KL, Moore DE, et al. Validation of the Written Administration of the Short Literacy Survey. *J Health Commun* 2015;20(7):835-842. doi: 10.1080 /10810730.2015.1018572
71. Bull FC, Maslin TS, & Armstrong T. Global Physical Activity Questionnaire (GPAQ): Nine Country Reliability and Validity Study. *J Phys Activ Health* 2009;6(6):790-804.
72. Hlatky MA , Boineau RE , Higginbotham MB , et al . A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651–4.
73. Dillon CB, Fitzgerald AP, Kearney PM, et al. Number of Days Required to Estimate Habitual Activity Using Wrist-Worn GENEActiv Accelerometer: A Cross-Sectional Study. *PLOS ONE* 2016;11(5):e0109913. doi: 10.1371/journal.pone.0109913
74. Moore CG, Carter RE, Nietert PJ, et al. Recommendations for Planning Pilot Studies in Clinical and Translational Research. *J Clin Transl Sci* 2011;4(5):332-37. doi: 10.1111/j.1752-8062.2011.00347.x
75. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65(3):301-8. doi: 10.1016/j.jclinepi.2011.07.011 [published Online First: 2011/12/16]

Tables and Figures

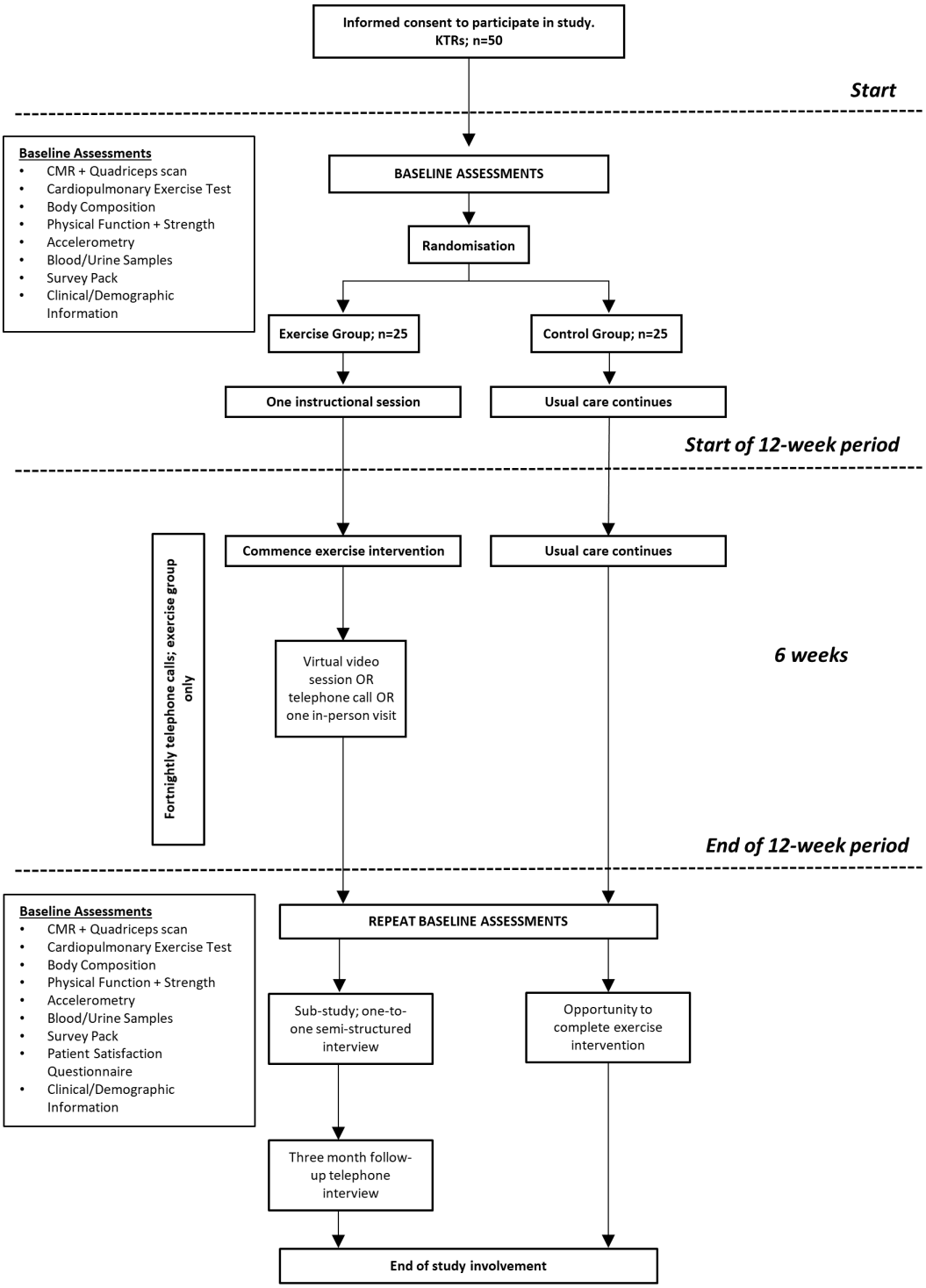

Figure 1. ECSERT study flow diagram

Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria

• Prevalent KTR >1 year
• Male or female, aged >18 years old
• Willing and able to give informed consent for participation in the study
• Increased cardiometabolic risk with at least one of:
  • Diabetes mellitus
  • Dyslipidaemia
  • Hypertension
  • Obesity (BMI >30)
  • History of ischaemic heart disease/cerebrovascular disease
	• Inability to give informed consent or comply with testing and exercise protocol for any reason
	• Unable to undergo CMR scanning (incompatible implants, claustrophobia, allergy to agents etc.)
	• Female participants who are pregnant, lactating, or planning pregnancy during the course of the study
	• Scheduled elective surgery or other procedures requiring general anaesthesia during the study
	• Any other significant disease or disorder*

*i.e. significant co-morbidity including unstable hypertension, potentially lethal arrhythmia, myocardial infarction within 6 months, unstable angina, active liver disease, uncontrolled diabetes mellitus (HbA1c ≥ 9%), advanced cerebral or peripheral vascular disease which, in the opinion of the patient's own clinician, may either put the patient at risk because of participation in the study, or may influence the result of the study, or the patient's ability to participate in the study.

Additional file details

File name: Additional File 1

File format: Additional File 1.pdf

Title of data: Original ECSERT flow diagram (pre-COVID-19)

Description of data: Flow diagram prior to COVID-19 amendments

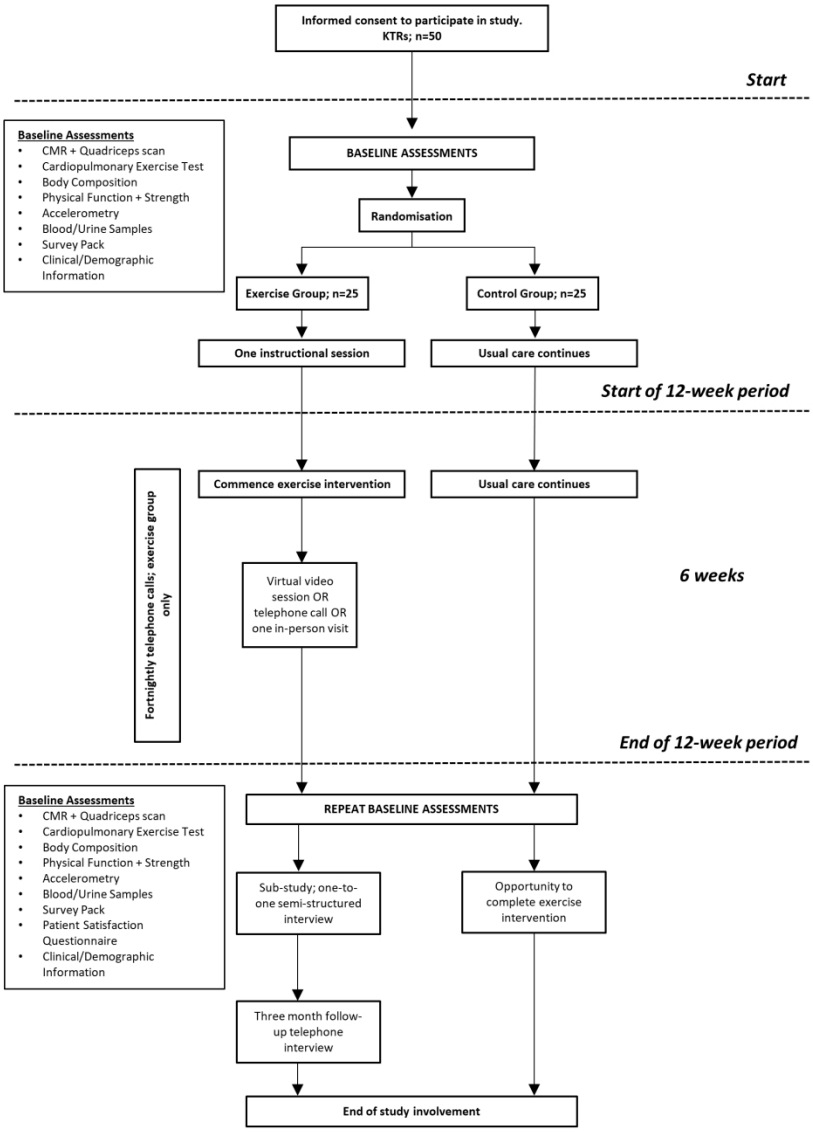

Figure 1. ECSERT study flow diagram

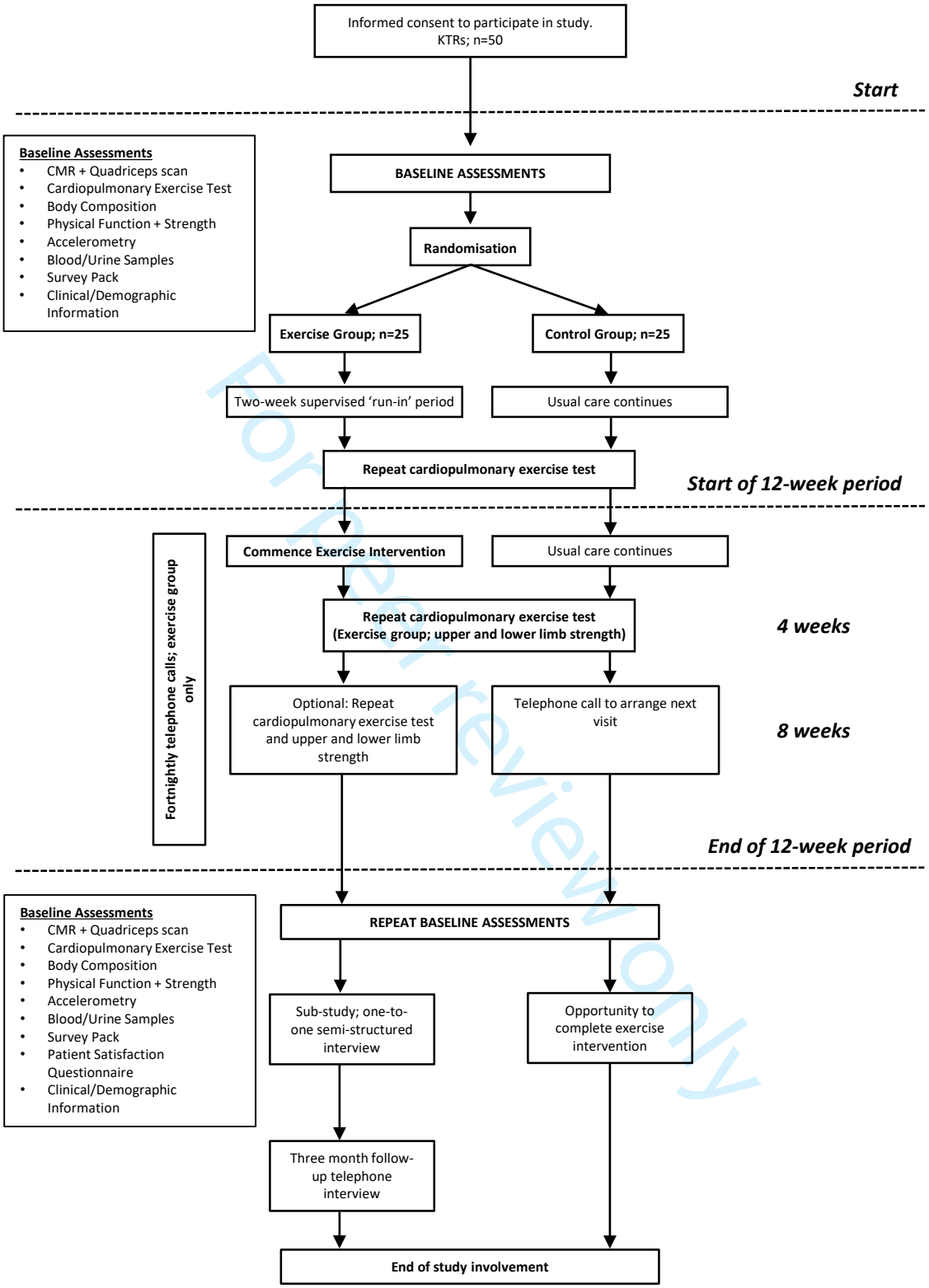

Figure X. Original ECSERT study flow diagram (pre-COVID-19)

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1, lines 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 2, lines 67)
	2b	All items from the World Health Organization Trial Registration Data Set (Yes, throughout)
Protocol version	3	Date and version identifier (page 16, line 494)
Funding	4	Sources and types of financial, material, and other support (page 16, line 506 and page 16, lines 511-513)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (page 1 and 15)
	5b	Name and contact information for the trial sponsor (page 16, line 488)
	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 (page 16, 506-509)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) N/A
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Introduction, page 3)
	6b	Explanation for choice of comparators (Introduction, page 3)
Objectives	7	Specific objectives or hypotheses (Page 4)

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) (Page 5)
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 (Page 5, line 141-143)
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) (Table 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 5 and 6)
	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) (Page 6, lines 176-178)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 10, lines 323-327)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 5, line 164)
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 (Study timeline, page 7)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 11, lines 346-348)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 5, 140+)
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 (Page 5, 154-159)
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 (Page 5, 154-159)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Page 5, 158)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A

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 (Page 7-11)
	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 (Page 11)
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 (Page 11, lines 349-354)
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 (Page 11 and 12)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A

	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) (Page 12)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC) or Data and Safety Monitoring Board (DCMB); 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 A DSMB is indicated, from a practical perspective in the following circumstances: 1. If the trial is intended to provide definitive information about effectiveness and/or safety of a medical or bio-behavioral intervention 2. If there are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity 3. If the trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications 4. If it would ethically be important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed The ECSERT study does not meet any of these criteria as a pilot/feasibility study
	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 N/A
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 (Page 12, safety reporting)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A aside from usual sponsor audits
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 16, ethical issues)
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) (Page 16, ethical issues)

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (consent form)
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 (Page 11)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 16, line 515)
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 (Page 17, availability of data)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 17, availability of data)
	31b	Authorship eligibility guidelines and any intended use of professional writers (Page 17, availability of data)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 17, availability of data)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Yes
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 (Page 10)

*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

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046945.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2021
Complete List of Authors:	Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences Wilkinson, Thomas ; University of Leicester, Department of Health Sciences Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Brady, Emer; University of Leicester, Department of Cardiovascular Sciences Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology Cooper, Nicola; University of Leicester, Department of Health Sciences Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Smith, Alice; University of Leicester, Department of Health Sciences Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit

Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine, Cardiovascular medicine
Keywords:	Renal transplantation < NEPHROLOGY, CARDIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Roseanne E Billany[1,2], Noemi Vadaszy[3], Nicolette C Bishop[4], Thomas J Wilkinson[3], Sherna Adenwalla[1,2], Katherine A Robinson[1], Kathryn Croker[2], Emer M Brady[1], Joanne Wormleighton[5], Kelly Parke[1,5], Nicola J Cooper[3], Angela C Webster[6], Jonathan Barratt[1,2], Gerry P McCann[1], James O Burton[1,2,5], Alice C Smith[3], Matthew PM Graham-Brown[1,2]

[1] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[2] John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK
[3] Department of Health Sciences, University of Leicester, Leicester, UK
[4] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK
[5] Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK
[6] Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and Transplant Research, Westmead Hospital, Sydney, NSW, Australia.

Corresponding author:
Dr Matthew Graham-Brown
Department of Cardiovascular Sciences
University of Leicester
Leicester
United Kingdom
mgb23@leicester.ac.uk

Keywords: kidney transplantation, home-based exercise, cardiovascular disease, feasibility, cardiac MRI

Abstract: 300
Word count: 4402

ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population, evidence is limited, and physical activity levels and patient activation towards exercise and self-management are low. This pilot study will assess the feasibility of delivering a structured, home-based exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise program.

Methods and analysis: Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-based combined resistance and aerobic exercise intervention or; (2) the control; usual care. Intervention participants will have one introductory session for instruction and practice of the recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access to instructional videos. The study will evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, and the intervention implementation. Outcomes, to be assessed prior to randomisation and post-intervention, include: cardiac structure and function with stress-perfusion cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of cardiometabolic health, quality of life, and patient activation. These data will be used to inform the power calculations for future definitive trials.

Ethics and dissemination: The protocol was reviewed and given favourable opinion by the East Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be published in peer-reviewed academic journals and will be disseminated to the patient and public community via social media, newsletter articles, and presentations at conferences.

Trial registration number: NCT04123951; prospectively registered.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Data on the effects of exercise interventions on the cardiac structural and functional aspects of CVD in this population are lacking and baseline values of multiparametric cardiac magnetic resonance imaging in KTRs are previously undefined.
- This study uses a novel home-based exercise intervention with the potential to translate into a widespread, low-resource intervention compared to in-centre, supervised interventions that are costly and labour intensive.
- As it can be difficult to ensure control groups are not influenced to change their lifestyle as a result of being part of the study; control participants will be offered the intervention after completion of the study.
- This study will provide quantitative and qualitative feasibility and pilot data to inform a definitive randomised controlled trial that will explore longer-term engendered lifestyle change in this population in response to a complex, home-based, lifestyle intervention.
- Secondary outcome analysis will identify the putative cardiometabolic and muscular effects of the intervention, although these results would need confirming in adequately powered studies due to the small sample size of this pilot study.

BACKGROUND

Kidney transplantation is the preferred modality of renal replacement therapy for patients with end stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage over remaining on dialysis,[1] cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and graft loss.[2-4] Since 2015, mortality rates attributed to CVD have been rising.[4] Cardiovascular disease in kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,[3 5 6] which drive classical atheromatous coronary artery disease, and non-traditional risk factors resulting in pathological changes in cardiovascular structure and function that associate with mortality.[7] Immunosuppressive agents are well known to drive traditional[3] and non-traditional cardiometabolic risk factors.[8 9] Non-traditional cardiometabolic risk factors, including endothelial dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-mineral metabolism,[10-12] are of at least equal importance in the pathogenesis of CVD in KTRs.[7] This is further illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate cardiovascular risk in patients with chronic kidney disease (CKD);[11 13-15] coronary revascularisation does not improve outcomes for KTRs as it does in the general population[12] and cardiac events are more likely to be fatal in KTRs.[16]

Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”, is characterised by stereotypical changes in the cardiovascular structure and function of the heart such as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,[17] myocardial fibrosis,[18] and aortic stiffness[19]; all of which relate to poor cardiovascular outcomes.[20 21] Although structural and functional improvements of the heart and vessels have been seen post-transplantation in some studies,[22] others have shown no regression[23] and parameters such as LVH are independent factors for cardiac failure and mortality in KTRs.[15] Cardiac magnetic resonance imaging (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic function to be reproducible in patients with kidney disease,[24-26] making CMR the ideal imaging modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.

Numerous epidemiological studies have observed the association between low levels of physical activity and increased prevalence of CVD risk factors,[27-29] and an inverse relationship between physical activity and all-cause and CVD mortality.[30 31] Physical activity levels in KTRs are lower than the general population,[32 33] with only 27% classified as meeting the UK national recommended physical activity levels.[34] Whilst physical activity levels improve in the year following transplantation, they plateau after one-year.[33] In the general population, lifestyle changes that increase physical activity through structured exercise lower mortality.[35 36] Despite this evidence, there is a lack of rigorous research into

the role of increased physical activity in mitigating cardiovascular risk in KTRs.[37] Recent consensus recommendations from experts and stakeholders highlighted the need for a priority research agenda in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this patient population.[38] Whilst supervised exercise interventions in KTRs improve cardiorespiratory fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic profile,[39-41] strength,[42] vascular stiffening,[40] weight,[43] and inflammation,[44] they are not realistically deliverable in the current financial climate and have not translated to clinical practice. Furthermore, exercise habits following in-centre supervised programs are not maintained[45-47] which can be potentially attributed to low levels of patient activation (a measure of a person's skills, confidence, and knowledge to manage their own health) and a failure for such programs to engender sustained lifestyle changes.[48 49] Home-based exercise training programs have been shown to be deliverable in patients on dialysis and patients undergoing cardiac rehabilitation,[50-53] but the effectiveness and deliverability of home-based exercise interventions are largely untested in KTRs. It cannot be assumed that such programs will be acceptable to KTRs, whose home-lives, social and occupational circumstances are significantly different to dialysis and cardiac patients. Many KTRs have had enforced sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes at work may be different.[54 55]

Objectives

The aims of this study are to evaluate the impact of a 12-week, home-based exercise intervention in KTRs with increased cardiometabolic risk, specifically addressing:

1. The deliverability and feasibility of the home-based exercise intervention in KTRs, defining recruitment, retention,compliance, and adverse events;
2. Potential cardiovascular structural and functional parameters measured using stress-perfusion CMR;
3. Cardiorespiratory fitness and strength;
4. Biochemical markers of cardiometabolic health, body composition, physical function, and quality of life;
5. Patient activation and continued adherence to the prescribed home-based exercise program.

Two sub-studies will assess:

1. The acceptability of the intervention through qualitative semi-structured interviews post-intervention.
2. The differences between cardiorespiratory fitness in 'healthy controls' versus KTRs.

METHODS AND ANALYSIS

ECSERT trial design

This study is a prospective, randomised, open-label, blinded endpoint (PROBE) pilot study. The study flowchart is presented in Figure 1.

Participant identification and recruitment

Fifty KTRs with a stable kidney transplant of >1 year will be recruited from University Hospitals of Leicester NHS Trust (UHL) kidney transplant outpatient clinic lists. There are approximately 400-420 KTRs registered in UHL kidney transplant outpatient clinics. Full lists of inclusion and exclusion criteria for KTRs are included in Table 1. Patients will be screened by a clinician for eligibility to enter the study. Eligible patients will be approached (via telephone, post, or during their routine clinical appointment) and will be provided with verbal and written study information and time to consider without further contact (at least 24 h). Additionally, eligible patients who have given prior consent to be contacted regarding research opportunities will be contacted via post. All patients will be given the opportunity to discuss the study in more detail and to consider their participation. Consent will be performed by the Chief Investigator (MBG) according to the rules of good clinical practice. Inclusion and exclusion criteria for healthy controls is included within Table 1.

Randomisation

Following baseline assessment, participants will be randomly allocated (1:1) to either; (1) a 12-week home-based combined resistance and aerobic exercise intervention (n=25) or; (2) control (n=25; receiving usual care). Randomisation will be blocked (using computer-generated random permuted blocks with allocation concealment; https://www.sealedenvelope.com/simple-randomiser/v1/) to ensure periodic balancing. The Clinical Trials Facilitator will perform the randomisation. Given the nature of the intervention, it is not possible for the participants to be blinded to their allocation.

Intervention and comparator arms

Intervention Group: 12-week home-based combined aerobic and resistance training

The 12-week, home-based, structured exercise program includes aerobic and resistance training (4-5 sessions in total per week). Participants will be advised to complete a warm-up and cool-down prior to and following each session, respectively. Participants will continue to receive usual clinical care.

Aerobic component

The aerobic component of the intervention will be walking, jogging, cycling, or similar, depending on resources available and participant preference. Participants will be asked to complete 2-3 sessions per week using a rating of perceived of exertion (RPE)[56] of 13-15 (somewhat hard) for 20-30 min. RPE will

be collected throughout cardiopulmonary exercise tests (CPET) and participants will be educated on its use during the instructional session(s). RPE will be utilised rather than heart rate for two reasons: (1) Many patients are on medication which impacts heart rate (e.g. beta-blockers). We therefore cannot ascertain a true maximal heart rate from the exercise test in order for them to safely (and reliably) monitor intensity this way without supervision. (2) This is a pragmatic decision based on the potential for translation into low-cost future studies and clinical practice. However, should participants in the trial already own a smart watch or heart rate monitor, we would not discourage them from using it if they desire.

Resistance component

The resistance component of the exercise intervention will include a combination of 6-8 exercises per session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row, reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has modifications for different abilities and may be pragmatically adjusted or changed throughout the study as required. These exercises were chosen based on their ability to be modified, their subjective difficulty, and their safety when being performed by participants new to exercise in an unsupervised environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of 10 repetitions (at approximately 60% of estimated 1 repetition maximum (RM)[57]), gradually increasing to 3-6 sets of 10 repetitions over the study period with a minimum of 30 sec rest between sets. These figures may be adjusted to accommodate different abilities and different rates of progression. Where equipment is limited (e.g. participants reach the highest provided dumbbell weight), participants will be advised to increase the number of sets performed. The load chosen was based on previous research which suggests whilst heavier loads (>60% of 1RM) are favoured for increasing strength, the effect size is still large for lighter loads (<60% of 1RM) and both are effective for increasing muscle size.[58] It is important not to discourage inactive or inexperienced participants with very heavy loads. Participants will be provided with an exercise diary which includes additional instructions, dumbbells and resistance bands, and access to educational and instructional videos. Instructional videos will include: the importance of an active and healthy lifestyle, the importance of warming up and cooling down and how to do it, a reminder of how to use the RPE scale, demonstrations of each resistance exercise, and information about the aerobic component (videos can be viewed here: https://www.youtube.com/playlist?list=PLwbE3AF9Ej_Vul5uoiF-C9Cl8wrgKz5Nv). Participants will receive a telephone call from a member of the research team every two weeks in order to discuss

progression of the exercise and address any issues that may arise. Participants will also be able to contact the research team at any time should they require and will continue to attend any scheduled clinic appointments and take prescribed medication as normal.

Control group: 'Usual care'

Participants in the control group will be asked to maintain their current lifestyle and exercise habits throughout the study. This includes continuing to attend any scheduled clinic appointments and taking prescribed medication as normal. As part of routine care, KTRs are recommended to take regular exercise and maintain a healthy lifestyle. This advice will be reiterated to patients in the control group to ensure the intervention is being appropriately compared to best-practice standard care. Participants will be asked to complete a 'control diary' to note any exercise, medication changes, illness, and other relevant information. Once control participants complete the post-intervention assessments, they will be offered the opportunity to complete the same intervention as the exercise group.

Study timeline

Baseline assessments

The ECSERT study timeline is shown in Figure 1. Baseline assessments described below will be carried out on the same day and in conjunction with routine clinical appointments to prevent additional travel.

Collection of routine clinical information and cost-effectiveness

Clinical information will be extracted from the medical notes including: age, gender, ethnicity, primary cause of kidney failure, transplant type, transplant vintage, dialysis duration, comorbidities, blood/urine results, current medication, and smoking habits. This information will be used to primarily capture cofounding variables and during analyses of differences and similarities between groups.

A questionnaire will be administered at baseline to capture the previous 3 months of self-reported healthcare utilisation including: inpatient and outpatient appointments, emergency care, community and primary care services, support services, and changes in medications. This will be compared to data gathered from healthcare records allowing validation of the questionnaire for future cost-effectiveness analyses.

Cardiac stress MRI

All participants will undergo a comprehensive adenosine-stress perfusion CMR scans at baseline and on study-completion. Participants will be scanned on a 3T platform (Skyra, Siemens Medical Imaging, Erlangen, Germany) with an 18-channel phased-array receiver coil. New-generation gadolinium-based

contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m^2 will be given for perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m^2 will undergo non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

- Left and right-ventricular structure and function (left ventricular mass, left and right ventricular volumes and ejection fractions);[59]
- Tissue-characterisation with native and post-contrast T1 mapping and delayed gadolinium enhancement;[60-62]
- Myocardial systolic-strain and peak early-diastolic strain rate;[26]
- Quantitative perfusion imaging (coronary blood-flow to quantify coronary reserve and ischaemia);[63]
- Aortic distensibility.[24]

Quadriceps MRI

At the end of the CMR scan, participants will immediately undergo an MRI scan of the quadriceps muscle in their right leg to assess muscle size (volume) as previously described[64]

Cardiopulmonary exercise test

A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W) every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min[65]. Participants will be encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured ($\dot{V}O_2$peak) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true maximal (plateau) $\dot{V}O_2$ ($\dot{V}O_2$max) is less commonly achieved in deconditioned and/or clinical patients. Test data will be considered usable if respiratory exchange ratio is ≥1.00 and RPE is ≥18. The test will be in the presence of a cardiac nurse to confirm safety to commence exercise training. Blood pressure will be assessed at baseline and every two minutes throughout the test. A continuous 12-lead electrocardiogram (ECG) will be monitored throughout. A non-invasive monitor (Moxy, Fortiori Design LLC., Minnesota, USA) will be worn on the quadriceps muscle which uses near infrared spectroscopy (NIRS) to measure local oxygen saturation (SmO_2) and total haemoglobin (THb) of the muscle.

Lower limb Strength and muscular endurance

Isometric and isokinetic muscle (knee extension) strength, of the dominant leg, will be assessed using a dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA). Peak isometric strength (torque, Nm) will be assessed from three repetitions of maximum effort at 90º knee flexion for ~3-5 sec with 60 sec rest. Isokinetic strength will be assessed at three speeds for one set of five

repetitions at each speed: 60°/sec, 90°/sec, and 120°/sec. Participants will perform a 'sit-to-stand-60' (STS-60) test measuring how many sit-to-stand cycles can be performed over 60 sec.

Handgrip strength

Peak grip strength of the left and right hands will be assessed with a hand dynamometer (Jamar Plus+; Sammons Preston, Bolingbrook, IL). Each hand will be alternatively tested for three attempts each and the highest value on each hand with be recorded.

Gait speed

A 4 m walk test will be used to assess gait speed. Participants will be asked to walk 4 m at their 'usual walking pace' for one practice and two, timed trials. The average score (m/sec) of the timed trials will be recorded.

Functional mobility

The 'timed-up-and-go' test (TUAG) will be used to assess functional mobility.[66 67] The participant is timed whilst rising from the seated position on a chair, walking 3 m, turning around, and returning to a seated position.

Balance and postural stability

Postural stability and balance will be assessed using a previously reported method[68] with a FysioMeter device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to software on a portable computer (FysioMeter ApS, Brønderslev, Denmark). Total centre of pressure ellipse area (mm^2) will be obtained.

Quadriceps ultrasound and myotonometry

Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D ultrasonography (Hitachi EUB-6500; probe frequency, 7.5 MHz) under resting conditions with the participant lying prone at a 45° as previously described.[64] Rectus femoris and vastus lateralis thickness, subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of the viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

Anthropometric measures

Anthropometric measures of height, body mass, and waist and hip circumference will be attained in accordance with standard protocols.[69] Bioelectrical impedance analysis (BIA) performed on an InBody analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat percentage, fat-free mass).[70 71]

Survey pack

Participants will be provided with a survey pack containing the following questionnaires:

(1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the presence and severity of disease related symptoms. The I-POS-Renal was developed based on the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms common in CKD such as pruritus and restless legs.[72]

(2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess generic health outcomes from the patient's perspective.[73]

(3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert scale that covers physical fatigue, functional fatigue, emotional fatigue, and social consequences of fatigue with excellent internal consistency and test-retest reliability.[74 75]

(4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval.[76]

(5) Patient Activation Measure (PAM): a validated, licenced tool measuring the spectrum of knowledge, skills, and confidence in patients and capturing the extent to which they feel engaged and confident in taking care of their condition ('activation').[77]

(6) Brief Health Literacy Screen (BHLS): a 3-item questionnaire to identify inadequate health literacy,[78] validated against longer screening tools in populations with ESKD.[79 80]

(7) The Global Physical Activity Questionnaire (GPAQ): developed by the World Health Organisation (WHO) for physical activity surveillance in countries. It collects information on physical activity participation in three settings or domains (activity at work, travel to and from places, and recreational activities) as well as sedentary behaviour, comprising 16 questions.[81]

(8) Duke Activity Status Index (DASI): a 12-item questionnaire that uses self-reported physical work capacity to estimate peak metabolic equivalents and has been shown to be a valid measurement of functional capacity.[82]

Habitual physical activity

Objective data on habitual physical activity levels over a 7-day period (ideal minimum 6-days)[83] will be gained from tri-axial accelerometers (GENEActiv, ActivInsights Ltd., Cambridge, UK). Participants will receive the monitor at the baseline and follow-up assessments and will be asked to wear it from midnight that evening for 7 days.

Blood and urine sampling

Venous blood (30 ml) will be collected using venepuncture of the antecubital vein and prepared and stored appropriately for the following analysis:

- Circulating markers of cardiovascular disease
- Circulating markers of systemic inflammation and oxidative stress
- Blood glucose and HbA1c
- Lipids and triglycerides
- Full blood count and renal profile

A urine sample will be requested to ascertain urinary protein:creatinine ratio.

Follow-up assessments

Follow up visits are summarised in Figure 1. An instructional session (or more if required) following baseline assessments will allow the intervention group to become familiar with the exercise requirements and allow the research team to ensure safety and competence before commencing the 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-week period for the intervention group only, participants will be invited to review exercise progression (via video call or in-person), particularly if participants are struggling to undertake the requisite amount of exercise, and as a refresher of the intervention. This combined with regular contact from research staff should aid participant compliance and monitoring.

Final assessments will be conducted for the exercise and control groups within 7 days of completing the 12-week exercise or control period. Assessments completed will be identical to the baseline visit with the addition of a 'patient satisfaction questionnaire' to allow pragmatic future development of the study. This will also be offered to participants who withdraw from the trial. Three months after completing the exercise intervention, participants will be contacted for a semi-structured one-to-one telephone interview. This will aim to understand the impact of the intervention, if any, on subsequent lifestyle and exercise habits.

Sub-studies

Additional informed consent will be sought for:

1. Ten 'healthy' control participants to undertake a CPET to assess the differences, if any, between CPET parameters in 'healthy controls' versus KTRs, particularly during the recovery period.
2. KTRs completing the exercise intervention will be invited to undertake a semi-structured interview (via telephone, video call, or in-person) incorporating exercise self-efficacy, enjoyment, difficulties encountered, perceived advantages and disadvantages of the

intervention, and study design. Participants who withdraw before the end of the intervention will also be invited to attend, although in line with ethical standards, this will be optional.

Sample size

The purpose of this pilot study is to obtain appropriate data to adequately power future definitive trials;[84] a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on accepted values to provide adequate estimates of standard deviations for future power calculations.[85]

Data collection and management

Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will be entered into a secure database and will only be accessible on password-protected computers at UHL and University of Leicester by relevant members of the study team. No identifying information will be kept in electronic form. All source data and original participant identities will be kept in a locked office in the trial site file only at UHL.

Data analysis

Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous data to be expressed as mean (± standard deviation), if normally distributed or median (interquartile range) if not. To investigate the differences between interventions we will use analysis of (co-) variance. Independent samples t-tests and Mann-Whitney U tests will be used assess for baseline differences between variables for normally and non-normally distributed data respectively. These data will be used to inform the power calculation for future definitive trials.

Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive thematic analysis to explore themes emerging from patient journeys through, and experiences of, the interventions and outcome measures.

Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

- *Eligibility:* the percentage of patients screened who are eligible.
- *Recruitment rate:* the percentage of patients eligible who consent to the trial and the monthly recruitment rate.
- *Adherence to the exercise intervention:* the number of completed sessions per week and specific intensity and durations achieved.
- *Acceptability of randomisation:* comparison of the final group characteristics and identification of any stratification variables, if applicable.
- *Attrition rate:* the number of participants that drop-out of the study.
- *Outcome acceptability:* the percentage of missing data for each outcome measure.

- *Safety:* The number of self-reported injuries or adverse events throughout the trial.

The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility (≥50%), recruitment success of 20% of eligible participants (≥2 participants per month), adherence (an average of 3 exercise sessions per week) and attrition (≤30%).

Safety reporting

All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) or serious adverse reactions (SARs) will be recorded from the time a patient enters the study to the final study visit. Each AE or AR will be considered for severity, causality, and expectedness and may be reclassified as an SAE or SAR if required.

An SAE is any AE that:

- is life threatening
- requires hospitalization or prolongation of a hospital admission
- results in a persistent or significant disability/incapacity
- is a congenital anomaly
- results in death

All AEs and ARs will be documented in participants CRFs, medical notes, and an AE log and will record the following information: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Only AEs that are judged to be related to the study intervention or procedures will be reported to the sponsor.

All SAEs will be reported by the investigators to the sponsor within 24 hours of discovery or notification and the report will be signed by the chief investigator within 7 days. If the SAE is deemed related to the research procedures or intervention and is unexpected, a report will be sent to the research ethics committee (REC) within 15 days.

Patient and public involvement

A patient and public involvement (PPI) group has been convened and will meet with the research team to review progress and address issues that arise throughout the duration of the study. The PPI partners will assist in the interpretation and dissemination of results. The trial was designed in consultation with PPI partners who advised on intervention content and outcome measure acceptability, paying particular attention to patient burden, ensuring outcome measures would not over-burden participants. The PPI group approved the final design and duration of this intervention and advised the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise capability.

Changes to the study protocol following the COVID-19 pandemic

The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst patient safety remains the absolute priority of clinical and research teams, there is a need for research to continue in a safe way that balances the benefits of continuing programs of research against the risks from COVID-19. We have amended the study protocol in several ways to reduce any additional exposure of patients to clinical environments where COVID-19 may be present:

- We have reduced the number of study visits to a minimum. The original study flow diagram is included in Additional file 1. All interim assessments have been removed in the modified protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient clinical care. That is to say, when they attend for their baseline and follow-up study visits they will have their clinical review and clinical blood tests as they would for their normal clinical care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical environment over-and-above their normal care.
- The original study design included a 2-week face-to-face training period where participants would attend the hospital to learn how to complete the exercises and the exercise program with a member of the research team. This training period will now be done remotely, via video conferencing, with discussion and feedback over the telephone and using the instructional videos and literature that support the home-based exercise intervention.
- When participants attend for their study visits, departmental procedures have been updated to now include meticulous cleaning of all equipment before and after use, one-way flows of participants to ensure participants do not mix, and the use of personal protective equipment for all staff and participants.

The above changes have been agreed with the local REC and the study sponsor and have allowed recommencement of study recruitment and procedures.

DISCUSSION

This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR to evaluate the structural and functional changes of the heart in this at risk population.

Qualitative data will provide valuable personal perspectives on the acceptability of this specific exercise program. Transplant recipients experience complex medical journeys and are likely to have

specific unmet needs in the area of exercise and lifestyle. This will be valuable information for future randomised controlled trials (RCTs) and exercise guideline development.

Home-based intervention outcomes are reliant on accurate reporting by participants with regards to frequency, intensity, and duration of exercise performed. This under-reporting is often a limitation of unsupervised interventions. We will ensure participants are correctly advised of how to monitor and report their exercise completion throughout the trial and encourage this through telephone communications.

We anticipate that a positive outcome will lead to both an increased understanding of the specific exercise requirements of KTRs and the development of new programs that promote longer-term engendered lifestyle change that can be incorporated into standard practice with much lower financial implications than in-centre supervised rehabilitation.

DECLARATIONS

Ethical issues

University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). The first participant was recruited on 09/03/2020. The predicted study end date is 31/12/2022. This manuscript is quorate with the most recent approved protocol (version 6 26.08.2020). Relevant parties will be informed of any substantial protocol modifications. Steps have been taken when designing this protocol to minimise the ethical implications and ensure patient welfare. The study will comply with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research Governance Framework for Health and Social Care.

Dissemination: On completion the results of this study will be published in peer-reviewed journals and presented at national and international conferences. Contributions of all authors to manuscripts arising from this study will be made explicit in the relevant of each individual journal. Participant level data will be available following publication of results on request to the Chief Investigator. Results will also be disseminated to the patient and public community via social media and newsletter articles and presentations at patient conferences and forums, led by the patient partners. It is anticipated that the results of this study will inform future design of larger RCTs in this subject area and contribute to future specific physical activity guidelines in this population.

Twitter: REB, @RBillany; MGB, @DrMattGB.

Author contributions: MGB is the chief investigator for this trial. REB and MGB are responsible for the study design, study setup, completion of study visits, drafting the manuscript, revision of the manuscript, and finalising the manuscript. NCB, TJW, KAR, KC, EMB, NJC, ACW, JB, GPM, JOB, and ACS are responsible for the study design, drafting the manuscript, and revision of the manuscript. NV, SA, JW, and KP are responsible for completion of study visits, drafting the manuscript, and revision of manuscript.

Funding: This study is funded by a project grant from Kidney Research UK (ref: KS_RP_003_20180913). Neither the sponsor nor the funder had or will have any input into study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Acknowledgements: This research is supported by the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests: None declared.

Consent for publication: Not applicable.

REFERENCES

1. Oniscu GC, Brown H, Forsythe JLR. How great is the survival advantage of transplantation over dialysis in elderly patients? *Nephrol Dial Transpl* 2004;19(4):945-51. doi: 10.1093/ndt/gfh022
2. Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. *Nephron* 2016;132 Suppl 1:111-44. doi: 10.1159/000444819
3. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. *World J Transplant* 2015;5(4):183-95. doi: 10.5500/wjt.v5.i4.183
4. UK Renal Registry (2020) UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from renal.org/audit-research/annual-report
5. Kasiske BL, Guijarro C, Massy ZA, et al. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996;7(1):158-65
6. Carpenter MA, John A, Weir MR, et al. BP, cardiovascular disease, and death in the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *J Am Soc Nephrol* 2014;25(7):1554-62. doi: 10.1681/asn.2013040435
7. Mall G, Huther W, Schneider J, et al. Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrol Dial Transplant* 1990;5(1):39-44. doi: 10.1093/ndt/5.1.39
8. Bakri RS, Afzali B, Covic A, et al. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. *Clin Transpl* 2004;18(2):201-04. doi: 10.1111/j.1399-0012.2004.00156.x
9. Liefeldt L, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int* 2010;23(12):1191-204. doi: 10.1111/j.1432-2277.2010.01159.x
10. Van Laecke S, Malfait T, Schepers E, et al. Cardiovascular disease after transplantation: an emerging role of the immune system. *Transpl Int* 2018;31(7):689-99. doi: 10.1111/tri.13160
11. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 2007;50(3):217-24. doi: 10.1016/j.jacc.2007.03.037
12. Aalten J, Peeters SA, van der Vlugt MJ, et al. Is standardized cardiac assessment of asymptomatic high-risk renal transplant candidates beneficial? *Nephrol Dial Transplant* 2011;26(9):3006-12. doi: 10.1093/ndt/gfq822
13. Mansell H, Rosaasen N, Dean J, et al. Evidence of enhanced systemic inflammation in stable kidney transplant recipients with low Framingham risk scores. *Clin Transpl* 2013;27(4):E391-E99
14. Mansell H, Stewart SA, Shoker A. Validity of cardiovascular risk prediction models in kidney transplant recipients. *Sci World J* 2014;2014:750579. doi: 10.1155/2014/750579
15. Devine PA, Courtney AE, Maxwell AP. Cardiovascular risk in renal transplant recipients. *J Nephrol* 2019;32(3):389-99. doi: 10.1007/s40620-018-0549-4
16. Kasiske BL. Epidemiology of cardiovascular disease after renal transplantation. *Transplantation* 2001;72(6 Suppl):S5-8. doi: 10.1097/00007890-200109271-00003
17. de Albuquerque Suassuna P, Sanders-Pinheiro H, de Paula R. Uremic Cardiomyopathy: A New Piece in the Chronic Kidney Disease-Mineral and Bone Disorder Puzzle. *Front Med (Lausanne)* 2018;5:206-06. doi: 10.3389/fmed.2018.00206
18. Aoki J, Ikari Y, Nakajima H, et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 2005;67(1):333-40. doi: 10.1111/j.1523-1755.2005.00086.x
19. Mark PB, Doyle A, Blyth KG, et al. Vascular function assessed with cardiovascular magnetic resonance predicts survival in patients with advanced chronic kidney disease. *J Cardiovasc Magn R* 2008;10:39. doi: 10.1186/1532-429x-10-39

20. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47(1):186-92. doi: 10.1038/ki.1995.22
21. Foley RN, Parfrey PS, Harnett JD, et al. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995;5(12):2024-31
22. Ali A, Macphee I, Kaski JC, et al. Cardiac and vascular changes with kidney transplantation. *Indian J Nephrol* 2016;26(1):1-9. doi: 10.4103/0971-4065.165003
23. Patel RK, Mark PB, Johnston N, et al. Renal Transplantation Is Not Associated with Regression of Left Ventricular Hypertrophy: A Magnetic Resonance Study. *Clin J Am Soc Nephrol* 2008;3(6):1807-11. doi: 10.2215/cjn.01400308
24. Graham-Brown MPM, Adenwalla SF, Lai FY, et al. The reproducibility of cardiac magnetic resonance imaging measures of aortic stiffness and their relationship to cardiac structure in prevalent haemodialysis patients. *Clin Kidney J* 2018;11(6):864-73. doi: 10.1093/ckj/sfy042
25. Graham-Brown MPM, Rutherford E, Levelt E, et al. Native T1 mapping: inter-study, inter-observer and inter-center reproducibility in hemodialysis patients. *J Cardiovasc Magn R* 2017;19(1) doi: 10.1186/s12968-017-0337-7
26. Graham-Brown MP, Gulsin GS, Parke K, et al. A comparison of the reproducibility of two cine-derived strain software programmes in disease states. *Eur J Radiol* 2019;113:51-58. doi: 10.1016/j.ejrad.2019.01.026
27. Kriska AM, Saremi A, Hanson RL, et al. Physical activity, obesity, and the incidence of type 2 diabetes in a high-risk population. *Am J Epidemiol* 2003;158(7):669-75. doi: 10.1093/aje/kwg191
28. Stamatakis E, Gale J, Bauman A, et al. Sitting Time, Physical Activity, and Risk of Mortality in Adults. *J Am Coll Cardiol* 2019;73(16):2062-72. doi: doi:10.1016/j.jacc.2019.02.031
29. Koolhaas CM, Dhana K, Schoufour JD, et al. Impact of physical activity on the association of overweight and obesity with cardiovascular disease: The Rotterdam Study. *Eur J Prev Cardiol* 2017;24(9):934-41. doi: 10.1177/2047487317693952
30. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J* 2013;77(2):281-92. doi: 10.1253/circj.cj-13-0007
31. Barengo NC, Hu G, Lakka TA, et al. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 2004;25(24):2204-11. doi: 10.1016/j.ehj.2004.10.009
32. Nielens H, Lejeune TM, Lalaoui A, et al. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. *Nephrol Dial Transpl* 2001;16(1):134-40. doi: 10.1093/ndt/16.1.134
33. Dontje ML, de Greef MH, Krijnen WP, et al. Longitudinal measurement of physical activity following kidney transplantation. *Clin Transplant* 2014;28(4):394-402. doi: 10.1111/ctr.12325
34. Wilkinson TJ, Clarke AL, Nixon DGD, et al. Prevalence and correlates of physical activity across kidney disease stages: an observational multicentre study. *Nephrol Dial Transpl* 2019 doi: 10.1093/ndt/gfz235
35. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012;2(2):1143-211. doi: 10.1002/cphy.c110025
36. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. *J Appl Physiol* 2011;111(5):1497-504. doi: 10.1152/japplphysiol.00420.2011
37. Oguchi H, Tsujita M, Yazawa M, et al. The efficacy of exercise training in kidney transplant recipients: a meta-analysis and systematic review. *Clin Exp Nephrol* 2019;23(2):275-84. doi: 10.1007/s10157-018-1633-8
38. Mathur S, Janaudis-Ferreira T, Wickerson L, et al. Meeting Report: Consensus Recommendations for a Research Agenda in Exercise in Solid Organ Transplantation. *Am J Transplant* 2014;14(10):2235-45. doi: 10.1111/ajt.12874

39. Masajtis-Zagajewska A, Muras K, Nowicki M. Effects of a Structured Physical Activity Program on Habitual Physical Activity and Body Composition in Patients With Chronic Kidney Disease and in Kidney Transplant Recipients. *Exp Clin Transplant* 2019;17(2):155-64. doi: 10.6002/ect.2017.0305
40. O'Connor EM, Koufaki P, Mercer TH, et al. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients - A pilot randomised controlled trial. *PLoS One* 2017;12(2):e0171063. doi: 10.1371/journal.pone.0171063
41. Moraes Dias CJ, Anaisse Azoubel LM, Araujo Costa H, et al. Autonomic modulation analysis in active and sedentary kidney transplanted recipients. *Clin Exp Pharmacol Physiol* 2015;42(12):1239-44. doi: 10.1111/1440-1681.12481
42. Karelis AD, Hébert MJ, Rabasa-Lhoret R, et al. Impact of Resistance Training on Factors Involved in the Development of New-Onset Diabetes After Transplantation in Renal Transplant Recipients: An Open Randomized Pilot Study. *Can J Diabetes* 2016;40(5):382-88. doi: 10.1016/j.jcjd.2015.08.014
43. Roi GS, Stefoni S, Mosconi G, et al. Physical activity in solid organ transplant recipients: organizational aspects and preliminary results of the Italian project. *Transplant Proc* 2014;46(7):2345-9. doi: 10.1016/j.transproceed.2014.07.055
44. Romano G, Simonella R, Falleti E, et al. Physical training effects in renal transplant recipients. *Clin Transplant* 2010;24(4):510-4. doi: 10.1111/j.1399-0012.2009.01098.x
45. Kinnafick FE, Thogersen-Ntoumani C, Shepherd SO, et al. In It Together: A Qualitative Evaluation of Participant Experiences of a 10-Week, Group-Based, Workplace HIIT Program for Insufficiently Active Adults. *J Sport Exerc Psychol* 2018;40(1):10-19. doi: 10.1123/jsep.2017-0306
46. van Baar ME, Dekker J, Oostendorp RA, et al. Effectiveness of exercise in patients with osteoarthritis of hip or knee: nine months' follow up. *Ann Rheum Dis* 2001;60(12):1123-30. doi: 10.1136/ard.60.12.1123
47. Timmons JF, Griffin C, Cogan KE, et al. Exercise Maintenance in Older Adults 1 Year After Completion of a Supervised Training Intervention. *J Am Geriatr Soc* 2020;68(1):163-69. doi: 10.1111/jgs.16209
48. Hibbard JH, Greene J. What The Evidence Shows About Patient Activation: Better Health Outcomes And Care Experiences; Fewer Data On Costs. *Health Affairs* 2013;32(2):207-14. doi: 10.1377/hlthaff.2012.1061
49. Skolasky RL, Mackenzie EJ, Wegener ST, et al. Patient activation and adherence to physical therapy in persons undergoing spine surgery. *Spine (Phila Pa 1976)* 2008;33(21):E784-E91. doi: 10.1097/BRS.0b013e31818027f1
50. Baggetta R, D'Arrigo G, Torino C, et al. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: a secondary analysis of the EXCITE trial. *BMC Geriatr* 2018;18(1):248. doi: 10.1186/s12877-018-0938-5
51. Imran HM, Baig M, Erqou S, et al. Home-Based Cardiac Rehabilitation Alone and Hybrid With Center-Based Cardiac Rehabilitation in Heart Failure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019;8(16):e012779. doi:10.1161/JAHA.119.012779
52. Uchiyama K, Washida N, Morimoto K, et al. Home-based Aerobic Exercise and Resistance Training in Peritoneal Dialysis Patients: A Randomized Controlled Trial. *Sci Rep* 2019;9(1):2632. doi: 10.1038/s41598-019-39074-9
53. Aoike DT, Baria F, Kamimura MA, et al. Home-based versus center-based aerobic exercise on cardiopulmonary performance, physical function, quality of life and quality of sleep of overweight patients with chronic kidney disease. *Clin Exp Nephrol* 2018;22(1):87-98. doi: 10.1007/s10157-017-1429-2
54. Majchrzak KM, Pupim LB, Chen K, et al. Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days. *J Ren Nutr* 2005;15(2):217-24. doi: 10.1053/j.jrn.2004.08.002

55. Carvalho EV, Reboredo MM, Gomes EP, et al. Physical activity in daily life assessed by an accelerometer in kidney transplant recipients and hemodialysis patients. *Transplant Proc* 2014;46(6):1713-7. doi: 10.1016/j.transproceed.2014.05.019
56. Borg GA. Perceived exertion: a note on "history" and methods. *Med Sci Sports* 1973;5(2):90-3.
57. Brzycki M. Strength Testing—Predicting a One-Rep Max from Reps-to-Fatigue. *Journal of Physical Education, Recreation & Dance* 1993;64(1):88-90. doi: 10.1080/07303084.1993.10606684
58. Schoenfeld BJ, Grgic J, Ogborn D, et al. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-analysis. *J Strength Cond Res* 2017;31(12):3508-23. doi: 10.1519/jsc.0000000000002200
59. Hunold P, Vogt FM, Heemann UW, et al. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI--study in dialysis patients examined before and after dialysis. *J Cardiovasc Magn R* 2003;5(4):553-61. doi: 10.1081/jcmr-120025230
60. Graham-Brown MP, March DS, Churchward DR, et al. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016;90(4):835-44. doi: 10.1016/j.kint.2016.07.014
61. Xu HY, Yang ZG, Zhang Y, et al. Prognostic value of heart failure in hemodialysis-dependent end-stage renal disease patients with myocardial fibrosis quantification by extracellular volume on cardiac magnetic resonance imaging. *BMC Cardiovasc Disord* 2020;20(1):12. doi: 10.1186/s12872-019-01313-2
62. Graham-Brown MP, Singh AS, Gulsin GS, et al. Defining myocardial fibrosis in haemodialysis patients with non-contrast cardiac magnetic resonance. *BMC Cardiovasc Disord* 2018;18(1):145. doi: 10.1186/s12872-018-0885-2
63. Xue H, Brown LAE, Nielles-Vallespin S, et al. Automatic in-line quantitative myocardial perfusion mapping: Processing algorithm and implementation. *Magn Reson Med* 2020;83(2):712-30. doi: 10.1002/mrm.27954
64. Gould DW, Watson EL, Wilkinson TJ, et al. Ultrasound assessment of muscle mass in response to exercise training in chronic kidney disease: a comparison with MRI. *J Cachexia Sarcopenia Muscle* 2019;10(4):748-55. doi: 10.1002/jcsm.12429
65. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Resp Crit Care* 2003;167(2):211-77. doi: 10.1164/rccm.167.2.211
66. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x
67. Hadjiioannou I, Wong K, Lindup H, et al. Test-restest reliability for physical function measures in patients with chronic kidney disease. *J Ren Care* 2019 doi: 10.1111/jorc.12310
68. Wilkinson TJ, Nixon DGD, Smith AC. Postural stability during standing and its association with physical and cognitive functions in non-dialysis chronic kidney disease patients. *Int J Nephrol Urol* 2019;51(8):1407-14. doi: 10.1007/s11255-019-02192-4
69. Eston RG, Reilly T. Kinanthropometry and exercise physiology laboratory manual: tests, procedures, and data. 3rd ed. Abingdon: Routledge 2009.
70. Chertow GM, Lowrie EG, Wilmore DW, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995;6(1):75-81.
71. Macdonald JH, Marcora SM, Jibani M, et al. Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transpl* 2006;21(12):3481-7. doi: 10.1093/ndt/gfl432
72. Raj R, Ahuja K, Frandsen M, et al. Validation of the IPOS-Renal Symptom Survey in Advanced Kidney Disease: A Cross-sectional Study. *J Pain Symptom Manage* 2018;56(2):281-87. doi: 10.1016/j.jpainsymman.2018.04.006
73. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996:220-33.

74. Wang S-Y, Zang X-Y, Liu J-D, et al. Psychometric Properties of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) in Chinese Patients Receiving Maintenance Dialysis. *J Pain Symptom Manage* 2015;49(1):135-43. doi: 10.1016/j.jpainsymman.2014.04.011
75. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13(2):63-74. doi: 10.1016/s0885-3924(96)00274-6
76. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4
77. Hibbard JH, Stockard J, Mahoney ER, et al. Development of the Patient Activation Measure (PAM): Conceptualizing and Measuring Activation in Patients and Consumers. *Health Serv Res* 2004;39(4p1):1005-26. doi: 10.1111/j.1475-6773.2004.00269.x
78. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med* 2004;36(8):588-94
79. Cavanaugh KL, Osborn CY, Tentori F, et al. Performance of a brief survey to assess health literacy in patients receiving hemodialysis. *Clinical Kidney Journal* 2015;8(4):462-8. doi: https://dx.doi.org/10.1093/ckj/sfv037
80. Dageforde LA, Cavanaugh KL, Moore DE, et al. Validation of the written administration of the short literacy survey. *J Health Commun* 2015;20(7):835-42. doi: 10.1080/10810730.2015.1018572
81. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790
82. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64(10):651-4. doi: 10.1016/0002-9149(89)90496-7
83. Dillon CB, Fitzgerald AP, Kearney PM, et al. Number of Days Required to Estimate Habitual Activity Using Wrist-Worn GENEActiv Accelerometer: A Cross-Sectional Study. *PLOS ONE* 2016;11(5):e0109913. doi: 10.1371/journal.pone.0109913
84. Moore CG, Carter RE, Nietert PJ, et al. Recommendations for Planning Pilot Studies in Clinical and Translational Research. *J Clin Transl Sci* 2011;4(5):332-37. doi: 10.1111/j.1752-8062.2011.00347.x
85. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65(3):301-8. doi: 10.1016/j.jclinepi.2011.07.011

Tables and Figures

See uploaded.

Figure 1. ECSERT study flow diagram

Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
RTRs	

• Prevalent KTR >1 year
• Male or female, aged >18 years old
• Willing and able to give informed consent for participation in the study
• Increased cardiometabolic risk with at least one of:
  • Diabetes mellitus
  • Dyslipidaemia
  • Hypertension
  • Obesity (BMI >30)
  • History of ischaemic heart disease/cerebrovascular disease
	• Inability to give informed consent or comply with testing and exercise protocol for any reason
	• Unable to undergo CMR scanning (incompatible implants, claustrophobia, allergy to agents etc.)
	• Female participants who are pregnant, lactating, or planning pregnancy during the course of the study
	• Scheduled elective surgery or other procedures requiring general anaesthesia during the study
	• Any other significant disease or disorder*

Healthy controls	

• Age <18 years
• No documented history of major cardiorespiratory chronic condition
• None of the following cardiometabolic risk factors:
  • Diabetes mellitus
  • Dyslipidaemia
  • Hypertension
  • History of ischaemic heart disease/cerebrovascular disease
  • Obesity (BMI>30)
• Not on any medication
	• Unable to undertake exercise testing due to physical or psychological barriers
	• Scheduled elective surgery or other procedures requiring general anaesthesia during the study
	• Inability to give informed consent or comply with testing and exercise protocol for any reason
	• Any other significant disease or disorder*

*i.e. significant co-morbidity including unstable hypertension, potentially lethal arrhythmia, myocardial infarction within 6 months, unstable angina, active liver disease, uncontrolled diabetes mellitus (HbA1c ≥ 9%), advanced cerebral or peripheral vascular disease which, in the opinion of the patient's own clinician, may either put the patient at risk because of participation in the study, or may influence the result of the study, or the patient's ability to participate in the study.

Additional file details

File name: Additional File 1

File format: Additional File 1.pdf

Title of data: Original ECSERT flow diagram (pre-COVID-19)

Description of data: Flow diagram prior to COVID-19 amendments

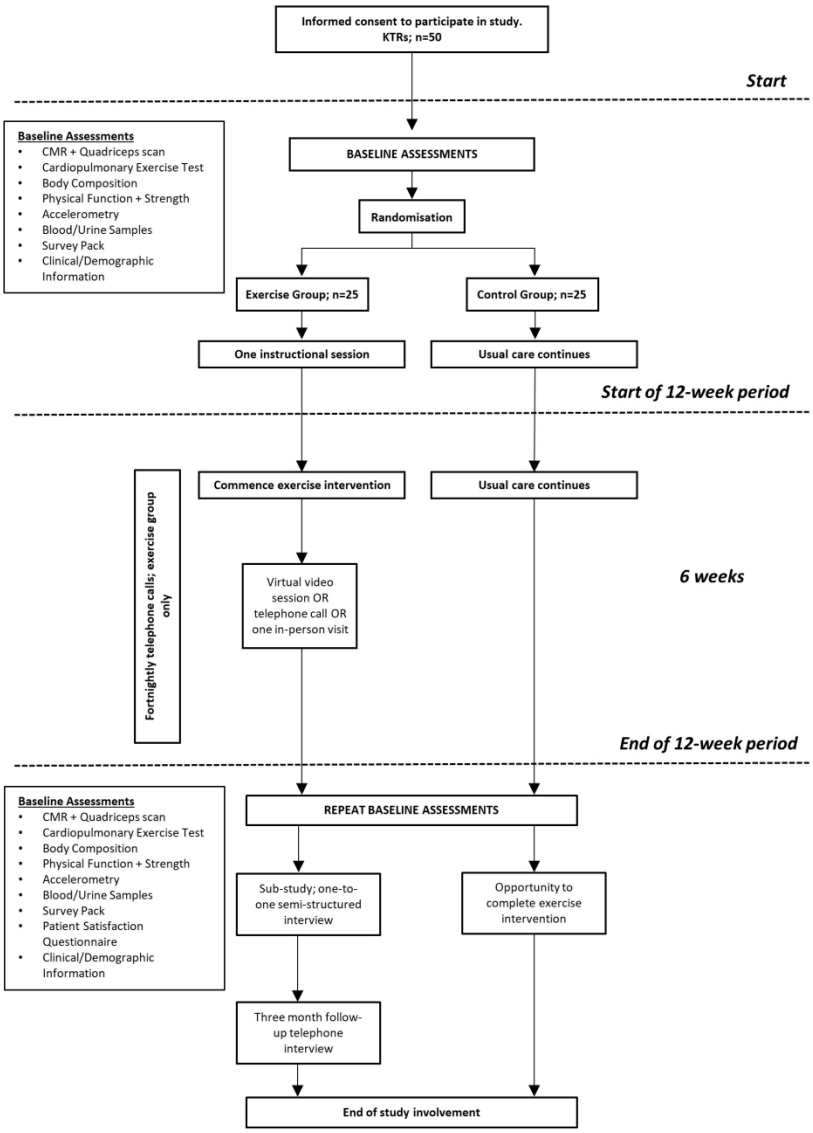

Figure 1 ECSERT Study Flow Diagram

170x219mm (300 x 300 DPI)

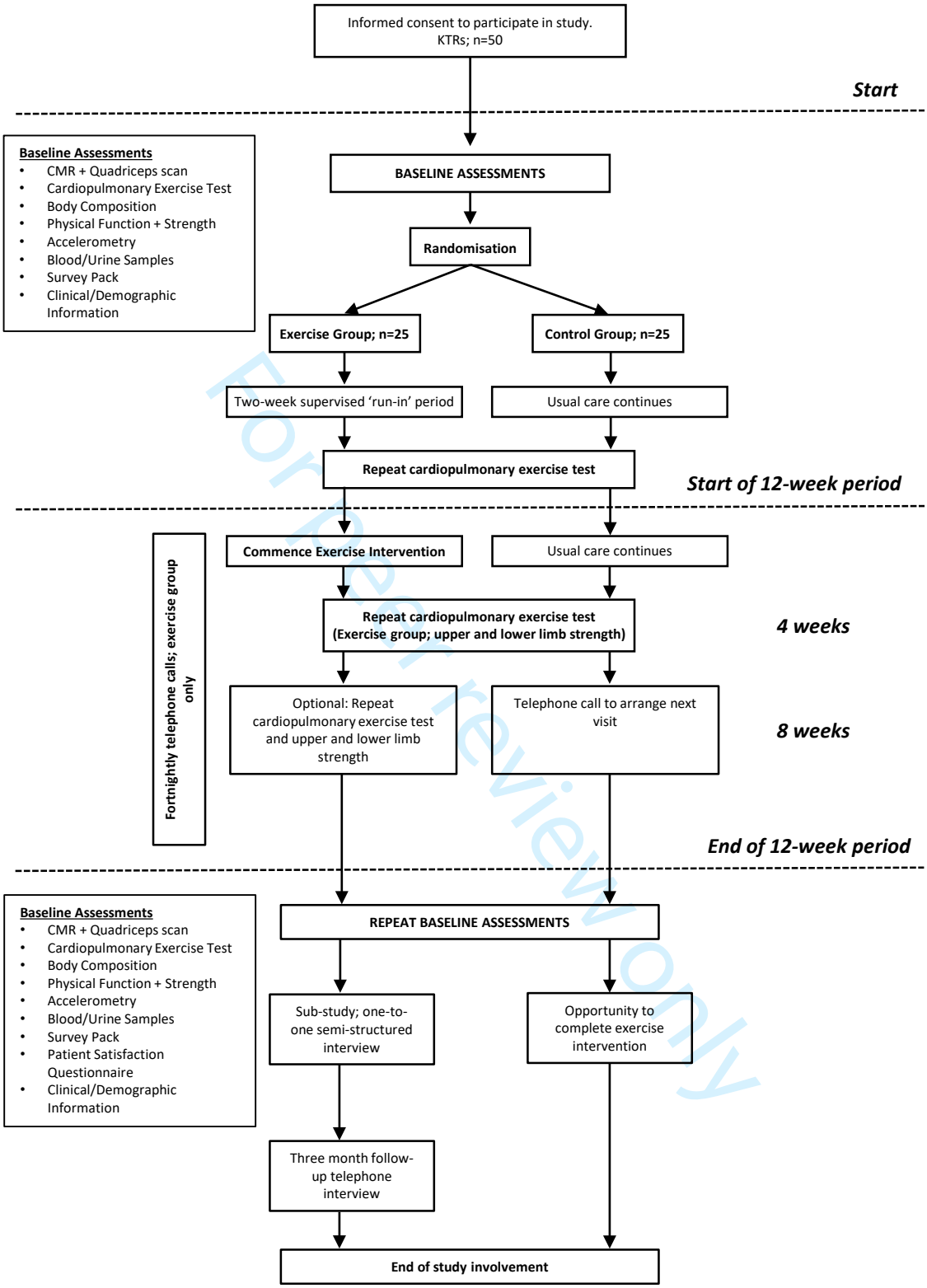

Figure X. Original ECSERT study flow diagram (pre-COVID-19)

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1, lines 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 2, lines 67)
	2b	All items from the World Health Organization Trial Registration Data Set (Yes, throughout)
Protocol version	3	Date and version identifier (page 16, line 494)
Funding	4	Sources and types of financial, material, and other support (page 16, line 506 and page 16, lines 511-513)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (page 1 and 15)
	5b	Name and contact information for the trial sponsor (page 16, line 488)
	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 (page 16, 506-509)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) N/A
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Introduction, page 3)
	6b	Explanation for choice of comparators (Introduction, page 3)
Objectives	7	Specific objectives or hypotheses (Page 4)

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) (Page 5)

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 (Page 5, line 141-143)
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) (Table 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 5 and 6)
	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) (Page 6, lines 176-178)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 10, lines 323-327)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 5, line 164)
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 (Study timeline, page 7)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 11, lines 346-348)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 5, 140+)

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 (Page 5, 154-159)
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 (Page 5, 154-159)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Page 5, 158)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
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 (Page 7-11)
	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 (Page 11)
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 (Page 11, lines 349-354)
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 (Page 11 and 12)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A

	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) (Page 12)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC) or Data and Safety Monitoring Board (DCMB); 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 A DSMB is indicated, from a practical perspective in the following circumstances: 1. If the trial is intended to provide definitive information about effectiveness and/or safety of a medical or bio-behavioral intervention 2. If there are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity 3. If the trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications 4. If it would ethically be important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed The ECSERT study does not meet any of these criteria as a pilot/feasibility study
	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 N/A
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 (Page 12, safety reporting)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A aside from usual sponsor audits
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 16, ethical issues)
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) (Page 16, ethical issues)

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (consent form)
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 (Page 11)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 16, line 515)
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 (Page 17, availability of data)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 17, availability of data)
	31b	Authorship eligibility guidelines and any intended use of professional writers (Page 17, availability of data)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 17, availability of data)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Yes
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 (Page 10)

*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

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046945.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Aug-2021
Complete List of Authors:	Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences Wilkinson, Thomas ; University of Leicester, Department of Health Sciences Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Brady, Emer; University of Leicester, Department of Cardiovascular Sciences Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology Cooper, Nicola; University of Leicester, Department of Health Sciences Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit Smith, Alice; University of Leicester, Department of Health Sciences Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit

Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine, Cardiovascular medicine
Keywords:	Renal transplantation < NEPHROLOGY, CARDIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A pilot randomised controlled trial of a structured, home-based exercise program on cardiovascular structure and function in kidney transplant recipients: The ECSERT study design and methods

Roseanne E Billany[1,2], Noemi Vadaszy[3], Nicolette C Bishop[4], Thomas J Wilkinson[3], Sherna F Adenwalla[1,2], Katherine A Robinson[1], Kathryn Croker[2], Emer M Brady[1], Joanne Wormleighton[5], Kelly Parke[1,5], Nicola J Cooper[3], Angela C Webster[6], Jonathan Barratt[1,2], Gerry P McCann[1], James O Burton[1,2,5], Alice C Smith[3], Matthew PM Graham-Brown[1,2]

[1] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[2] John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK
[3] Department of Health Sciences, University of Leicester, Leicester, UK
[4] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK
[5] Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK
[6] Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and Transplant Research, Westmead Hospital, Sydney, NSW, Australia.

Corresponding author:
Dr Matthew Graham-Brown
Department of Cardiovascular Sciences
University of Leicester
Leicester
United Kingdom
mgb23@leicester.ac.uk

Keywords: kidney transplantation, home-based exercise, cardiovascular disease, feasibility, cardiac MRI

Abstract: 300
Word count: 4402

ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population, evidence is limited, and physical activity levels and patient activation towards exercise and self-management are low. This pilot study will assess the feasibility of delivering a structured, home-based exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise program.

Methods and analysis: Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-based combined resistance and aerobic exercise intervention or; (2) the control; usual care. Intervention participants will have one introductory session for instruction and practice of the recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access to instructional videos. The study will evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, and the intervention implementation. Outcomes, to be assessed prior to randomisation and post-intervention, include: cardiac structure and function with stress-perfusion cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of cardiometabolic health, quality of life, and patient activation. These data will be used to inform the power calculations for future definitive trials.

Ethics and dissemination: The protocol was reviewed and given favourable opinion by the East Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be published in peer-reviewed academic journals and will be disseminated to the patient and public community via social media, newsletter articles, and presentations at conferences.

Trial registration number: NCT04123951; prospectively registered.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Data on the effects of exercise interventions on the cardiac structural and functional aspects of CVD in this population are lacking and baseline values of multiparametric cardiac magnetic resonance imaging in KTRs are previously undefined.
- This study uses a novel home-based exercise intervention with the potential to translate into a widespread, low-resource intervention compared to in-centre, supervised interventions that are costly and labour intensive.
- As it can be difficult to ensure control groups are not influenced to change their lifestyle as a result of being part of the study; control participants will be offered the intervention after completion of the study.
- This study will provide quantitative and qualitative feasibility and pilot data to inform a definitive randomised controlled trial that will explore longer-term engendered lifestyle change in this population in response to a complex, home-based, lifestyle intervention.
- Secondary outcome analysis will identify the putative cardiometabolic and muscular effects of the intervention, although these results would need confirming in adequately powered studies due to the small sample size of this pilot study.

BACKGROUND

Kidney transplantation is the preferred modality of renal replacement therapy for patients with end stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage over remaining on dialysis,[1] cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and graft loss.[2-4] Since 2015, mortality rates attributed to CVD have been rising.[4] Cardiovascular disease in kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,[3 5 6] which drive classical atheromatous coronary artery disease, and non-traditional risk factors resulting in pathological changes in cardiovascular structure and function that associate with mortality.[7] Immunosuppressive agents are well known to drive traditional[3] and non-traditional cardiometabolic risk factors.[8 9] Non-traditional cardiometabolic risk factors, including endothelial dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-mineral metabolism,[10-12] are of at least equal importance in the pathogenesis of CVD in KTRs.[7] This is further illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate cardiovascular risk in patients with chronic kidney disease (CKD);[11 13-15] coronary revascularisation does not improve outcomes for KTRs as it does in the general population[12] and cardiac events are more likely to be fatal in KTRs.[16]

Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”, is characterised by stereotypical changes in the cardiovascular structure and function of the heart such as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,[17] myocardial fibrosis,[18] and aortic stiffness[19]; all of which relate to poor cardiovascular outcomes.[20 21] Although structural and functional improvements of the heart and vessels have been seen post-transplantation in some studies,[22] others have shown no regression[23] and parameters such as LVH are independent factors for cardiac failure and mortality in KTRs.[15] Cardiac magnetic resonance imaging (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic function to be reproducible in patients with kidney disease,[24-26] making CMR the ideal imaging modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.

Numerous epidemiological studies have observed the association between low levels of physical activity and increased prevalence of CVD risk factors,[27-29] and an inverse relationship between physical activity and all-cause and CVD mortality.[30 31] Physical activity levels in KTRs are lower than the general population,[32-34] with only 27% classified as meeting the UK national recommended physical activity levels.[35] Whilst physical activity levels improve in the year following transplantation, they plateau after one-year.[33] In the general population, lifestyle changes that increase physical activity through structured exercise lower mortality.[36 37] Despite this evidence, there is a lack of rigorous research into

the role of increased physical activity in mitigating cardiovascular risk in KTRs.[38] Recent consensus recommendations from experts and stakeholders highlighted the need for a priority research agenda in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this patient population.[39] Whilst supervised exercise interventions in KTRs improve cardiorespiratory fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic profile,[40-42] strength,[43] vascular stiffening,[41] weight,[44] and inflammation,[45] they are not realistically deliverable in the current financial climate and have not translated to clinical practice. Furthermore, exercise habits following in-centre supervised programs are not maintained[46-48] which can be potentially attributed to low levels of patient activation (a measure of a person's skills, confidence, and knowledge to manage their own health) and a failure for such programs to engender sustained lifestyle changes.[49 50] Home-based exercise training programs have been shown to be deliverable in patients on dialysis and patients undergoing cardiac rehabilitation,[51-54] but the effectiveness and deliverability of home-based exercise interventions are largely untested in KTRs. It cannot be assumed that such programs will be acceptable to KTRs, whose home-lives, social and occupational circumstances are significantly different to dialysis and cardiac patients. Many KTRs have had enforced sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes at work may be different.[55 56]

Objectives

The aims of this study are to evaluate the impact of a 12-week, home-based exercise intervention in KTRs with increased cardiometabolic risk, specifically addressing:

1. The deliverability and feasibility of the home-based exercise intervention in KTRs, defining recruitment, retention,compliance, and adverse events;
2. Potential cardiovascular structural and functional parameters measured using stress-perfusion CMR;
3. Cardiorespiratory fitness and strength;
4. Biochemical markers of cardiometabolic health, body composition, physical function, and quality of life;
5. Patient activation and continued adherence to the prescribed home-based exercise program.

Two sub-studies will assess:

1. The acceptability of the intervention through qualitative semi-structured interviews post-intervention.
2. The differences between cardiorespiratory fitness in 'healthy controls' without a kidney transplant versus KTRs.

METHODS AND ANALYSIS

ECSERT trial design

This study is a prospective, randomised, open-label, blinded endpoint (PROBE) pilot study. The study flowchart is presented in Figure 1.

Participant identification and recruitment

Fifty KTRs with a stable kidney transplant of >1 year will be recruited from University Hospitals of Leicester NHS Trust (UHL) kidney transplant outpatient clinic lists. There are approximately 400-420 KTRs registered in UHL kidney transplant outpatient clinics. Full lists of inclusion and exclusion criteria for KTRs are included in Table 1. Patients will be screened by a clinician for eligibility to enter the study. Eligible patients will be approached (via telephone, post, or during their routine clinical appointment) and will be provided with verbal and written study information and time to consider without further contact (at least 24 h). Additionally, eligible patients who have given prior consent to be contacted regarding research opportunities will be contacted via post. All patients will be given the opportunity to discuss the study in more detail and to consider their participation. Consent will be performed by the Chief Investigator (MBG) according to the rules of good clinical practice. Inclusion and exclusion criteria for healthy controls is included within Table 1.

Randomisation

Following baseline assessment, participants will be randomly allocated (1:1) to either; (1) a 12-week home-based combined resistance and aerobic exercise intervention (n=25) or; (2) control (n=25; receiving usual care). Randomisation will be blocked (using computer-generated random permuted blocks with allocation concealment; https://www.sealedenvelope.com/simple-randomiser/v1/) to ensure periodic balancing. The Clinical Trials Facilitator will perform the randomisation. Given the nature of the intervention, it is not possible for the participants to be blinded to their allocation.

Intervention and comparator arms

Intervention Group: 12-week home-based combined aerobic and resistance training

The 12-week, home-based, structured exercise program includes aerobic and resistance training (4-5 sessions in total per week). Participants will be advised to complete a warm-up and cool-down prior to and following each session, respectively. Participants will continue to receive usual clinical care.

Aerobic component

The aerobic component of the intervention will be walking, jogging, cycling, or similar, depending on resources available and participant preference. Participants will be asked to complete 2-3 sessions per week using a rating of perceived of exertion (RPE)[57] of 13-15 (somewhat hard) for 20-30 min. RPE will be collected throughout cardiopulmonary exercise tests (CPET) and participants will be educated on its use during the instructional session(s). RPE will be utilised rather than heart rate for two reasons: (1) Many patients are on medication which impacts heart rate (e.g. beta-blockers). We therefore cannot ascertain a true maximal heart rate from the exercise test in order for them to safely (and reliably) monitor intensity this way without supervision. (2) This is a pragmatic decision based on the potential for translation into low-cost future studies and clinical practice. However, should participants in the trial already own a smart watch or heart rate monitor, we would not discourage them from using it if they desire.

Resistance component

The resistance component of the exercise intervention will include a combination of 6-8 exercises per session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row, reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has modifications for different abilities and may be pragmatically adjusted or changed throughout the study as required. These exercises were chosen based on their ability to be modified, their subjective difficulty, and their safety when being performed by participants new to exercise in an unsupervised environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of 10 repetitions (at approximately 60% of estimated 1 repetition maximum (RM)[58]), gradually increasing to 3-6 sets of 10 repetitions over the study period with a minimum of 30 sec rest between sets. The 1RM will be determined after randomisation by an exercise physiologist. These figures may be adjusted to accommodate different abilities and different rates of progression. Where equipment is limited (e.g. participants reach the highest provided dumbbell weight), participants will be advised to increase the number of sets performed. The load chosen was based on previous research which suggests whilst heavier loads (>60% of 1RM) are favoured for increasing strength, the effect size is still large for lighter loads (<60% of 1RM) and both are effective for increasing muscle size.[59] It is important not to discourage inactive or inexperienced participants with very heavy loads. Participants will be provided with an exercise diary which includes additional instructions, dumbbells and resistance bands, and access to educational and instructional videos. Instructional videos will include: the importance of an active and healthy lifestyle, the importance of warming up and cooling down and

how to do it, a reminder of how to use the RPE scale, demonstrations of each resistance exercise, and information about the aerobic component (videos can be viewed here: https://www.youtube.com/playlist?list=PLwbE3AF9Ej_Vul5uoiF-C9Cl8wrgKz5Nv). Participants will receive a telephone call from a member of the research team every two weeks in order to discuss progression of the exercise and address any issues that may arise. Participants will also be able to contact the research team at time should they require and will continue to attend any scheduled clinic appointments and take prescribed medication as normal.

Control group: 'Usual care'

Participants in the control group will be asked to maintain their current lifestyle and exercise habits throughout the study. This includes continuing to attend any scheduled clinic appointments and taking prescribed medication as normal. As part of routine care, KTRs are recommended to take regular exercise and maintain a healthy lifestyle. This advice will be reiterated to patients in the control group to ensure the intervention is being appropriately compared to best-practice standard care. Participants will be asked to complete a 'control diary' to note any exercise, medication changes, illness, and other relevant information. Once control participants complete the post-intervention assessments, they will be offered the opportunity to complete the same intervention as the exercise group.

Study timeline

Baseline assessments

The ECSERT study timeline is shown in Figure 1. Baseline assessments described below will be carried out on the same day and in conjunction with routine clinical appointments to prevent additional travel.

Collection of routine clinical information and cost-effectiveness

Clinical information will be extracted from the medical notes including: age, gender, ethnicity, primary cause of kidney failure, transplant type, transplant vintage, dialysis duration, comorbidities, blood/urine results, current medication, and smoking habits. This information will be used to primarily capture cofounding variables and during analyses of differences and similarities between groups.

A questionnaire will be administered at baseline to capture the previous 3 months of self-reported healthcare utilisation including: inpatient and outpatient appointments, emergency care, community and primary care services, support services, and changes in medications. This will be compared to data gathered from healthcare records allowing validation of the questionnaire for future cost-effectiveness analyses.

Cardiac stress MRI

All participants will undergo a comprehensive adenosine-stress perfusion CMR scans at baseline and on study-completion. Participants will be scanned on a 3T platform (Skyra, Siemens Medical Imaging, Erlangen, Germany) with an 18-channel phased-array receiver coil. New-generation gadolinium-based contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m^2 will be given for perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m^2 will undergo non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

- Left and right-ventricular structure and function (left ventricular mass, left and right ventricular volumes and ejection fractions);[60]
- Tissue-characterisation with native and post-contrast T1 mapping and delayed gadolinium enhancement;[61-63]
- Myocardial systolic-strain and peak early-diastolic strain rate;[26]
- Quantitative perfusion imaging (coronary blood-flow to quantify coronary reserve and ischaemia);[64]
- Aortic distensibility.[24]

Quadriceps MRI

At the end of the CMR scan, participants will immediately undergo an MRI scan of the quadriceps muscle in their right leg to assess muscle size (volume) as previously described[65]

Cardiopulmonary exercise test

A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W) every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min[66]. Participants will be encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured ($\dot{V}O_2$peak) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true maximal (plateau) $\dot{V}O_2$ ($\dot{V}O_2$max) is less commonly achieved in deconditioned and/or clinical patients. Test data will be considered usable if respiratory exchange ratio is ≥1.00 and RPE is ≥18. The test will be in the presence of a cardiac nurse to confirm safety to commence exercise training. Blood pressure will be assessed at baseline and every two minutes throughout the test. A continuous 12-lead electrocardiogram (ECG) will be monitored throughout. A non-invasive monitor (Moxy, Fortiori Design LLC., Minnesota, USA) will be worn on the quadriceps muscle which uses near infrared spectroscopy (NIRS) to measure local oxygen saturation (SmO_2) and total haemoglobin (THb) of the muscle.

Lower limb Strength and muscular endurance

Isometric and isokinetic muscle (knee extension) strength, of the dominant leg, will be assessed using a dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA).[67] Peak isometric strength (torque, Nm) will be assessed from three repetitions of maximum effort at 90º knee flexion for ~3-5 sec with 60 sec rest. Isokinetic strength will be assessed at three speeds for one set of five repetitions at each speed: 60°/sec, 90°/sec, and 120°/sec. Participants will perform a 'sit-to-stand-60' (STS-60) test measuring how many sit-to-stand cycles can be performed over 60 seconds to assess lower limb muscular endurance.[68]

Handgrip strength

Peak grip strength of the left and right hands will be assessed with a hand dynamometer (Jamar Plus+; Sammons Preston, Bolingbrook, IL). Each hand will be alternatively tested for three attempts each and the highest value on each hand with be recorded.[69]

Gait speed

A 4 m walk test will be used to assess gait speed. Participants will be asked to walk 4 m at their 'usual walking pace' for one practice and two, timed trials. The average score (m/sec) of the timed trials will be recorded.

Functional mobility

The 'timed-up-and-go' test (TUAG) will be used to assess functional mobility.[70 71] The participant is timed whilst rising from the seated position on a chair, walking 3 m, turning around, and returning to a seated position.

Balance and postural stability

Postural stability and balance will be assessed using a previously reported method[72] with a FysioMeter device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to software on a portable computer (FysioMeter ApS, Brønderslev, Denmark). Total centre of pressure ellipse area (mm^2) will be obtained.

Quadriceps ultrasound and myotonometry

Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D ultrasonography (Hitachi EUB-6500; probe frequency, 7.5 MHz) under resting conditions with the participant lying prone at a 45° as previously described.[65] Rectus femoris and vastus lateralis thickness, subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of the viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

Anthropometric measures

Anthropometric measures of height, body mass, and waist and hip circumference will be attained in accordance with standard protocols.[73] Bioelectrical impedance analysis (BIA) performed on an InBody analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat percentage, fat-free mass).[74 75]

Survey pack

Participants will be provided with a survey pack containing the following questionnaires:

(1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the presence and severity of disease related symptoms. The I-POS-Renal was developed based on the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms common in CKD such as pruritus and restless legs.[76]

(2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess generic health outcomes from the patient's perspective.[77]

(3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert scale that covers physical fatigue, functional fatigue, emotional fatigue, and social consequences of fatigue with excellent internal consistency and test-retest reliability.[78 79]

(4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval.[80]

(5) Patient Activation Measure (PAM): a validated, licenced tool measuring the spectrum of knowledge, skills, and confidence in patients and capturing the extent to which they feel engaged and confident in taking care of their condition ('activation').[81]

(6) Brief Health Literacy Screen (BHLS): a 3-item questionnaire to identify inadequate health literacy,[82] validated against longer screening tools in populations with ESKD.[83 84]

(7) The Global Physical Activity Questionnaire (GPAQ): developed by the World Health Organisation (WHO) for physical activity surveillance in countries. It collects information on physical activity participation in three settings or domains (activity at work, travel to and from places, and recreational activities) as well as sedentary behaviour, comprising 16 questions.[85]

(8) Duke Activity Status Index (DASI): a 12-item questionnaire that uses self-reported physical work capacity to estimate peak metabolic equivalents and has been shown to be a valid measurement of functional capacity.[86]

Habitual physical activity

Objective data on habitual physical activity levels over a 7-day period (ideal minimum 6-days)[87] will be gained from tri-axial accelerometers (GENEActiv, ActivInsights Ltd., Cambridge, UK). Participants will receive the monitor at the baseline and follow-up assessments and will be asked to wear it from midnight that evening for 7 days.

Blood and urine sampling

Venous blood (30 ml) will be collected using venepuncture of the antecubital vein and prepared and stored appropriately for the following analysis:

- Circulating markers of cardiovascular disease
- Circulating markers of systemic inflammation and oxidative stress
- Blood glucose and HbA1c
- Lipids and triglycerides
- Full blood count and renal profile

A urine sample will be requested to ascertain urinary protein:creatinine ratio.

Follow-up assessments

Follow up visits are summarised in Figure 1. An instructional session (or more if required) following baseline assessments will allow the intervention group to become familiar with the exercise requirements and allow the research team to ensure safety and competence before commencing the 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-week period for the intervention group only, participants will be invited to review exercise progression (via video call or in-person), particularly if participants are struggling to undertake the requisite amount of exercise, and as a refresher of the intervention. This combined with regular contact from research staff should aid participant compliance and monitoring.

Final assessments will be conducted for the exercise and control groups within 7 days of completing the 12-week exercise or control period. Assessments completed will be identical to the baseline visit with the addition of a 'patient satisfaction questionnaire' to allow pragmatic future development of the study. This will also be offered to participants who withdraw from the trial. Three months after completing the exercise intervention, participants will be contacted for a semi-structured one-to-one telephone interview. This will aim to understand the impact of the intervention, if any, on subsequent lifestyle and exercise habits.

Sub-studies

Additional informed consent will be sought for:

1. Ten 'healthy' control participants to undertake a CPET to assess the differences, if any, between CPET parameters in 'healthy controls' versus KTRs, particularly during the recovery period.
2. KTRs completing the exercise intervention will be invited to undertake a semi-structured interview (via telephone, video call, or in-person) incorporating exercise self-efficacy, enjoyment, difficulties encountered, perceived advantages and disadvantages of the intervention, and study design. Participants who withdraw before the end of the intervention will also be invited to attend, although in line with ethical standards, this will be optional.

Sample size

The purpose of this pilot study is to obtain appropriate data to adequately power future definitive trials;[88] a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on accepted values to provide adequate estimates of standard deviations for future power calculations.[89]

Data collection and management

Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will be entered into a secure database and will only be accessible on password-protected computers at UHL and University of Leicester by relevant members of the study team. No identifying information will be kept in electronic form. All source data and original participant identities will be kept in a locked office in the trial site file only at UHL.

Data analysis

Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous data to be expressed as mean (± standard deviation), if normally distributed or median (interquartile range) if not. To investigate the differences between interventions we will use analysis of (co-) variance. Independent samples t-tests and Mann-Whitney U tests will be used assess for baseline differences between variables for normally and non-normally distributed data respectively. These data will be used to inform the power calculation for future definitive trials.

Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive thematic analysis to explore themes emerging from patient journeys through, and experiences of, the interventions and outcome measures.

Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

- *Eligibility:* the percentage of patients screened who are eligible.
- *Recruitment rate:* the percentage of patients eligible who consent to the trial and the monthly recruitment rate.

- *Adherence to the exercise intervention:* the number of completed sessions per week and specific intensity and durations achieved.
- *Acceptability of randomisation:* comparison of the final group characteristics and identification of any stratification variables, if applicable.
- *Attrition rate:* the number of participants that drop-out of the study.
- *Outcome acceptability:* the percentage of missing data for each outcome measure.
- *Safety:* The number of self-reported injuries or adverse events throughout the trial.

The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility (≥50%), recruitment success of 20% of eligible participants (≥2 participants per month), adherence (an average of 3 exercise sessions per week) and attrition (≤30%).

Safety reporting

All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) or serious adverse reactions (SARs) will be recorded from the time a patient enters the study to the final study visit. Each AE or AR will be considered for severity, causality, and expectedness and may be reclassified as an SAE or SAR if required.

An SAE is any AE that:

- is life threatening
- requires hospitalization or prolongation of a hospital admission
- results in a persistent or significant disability/incapacity
- is a congenital anomaly
- results in death

All AEs and ARs will be documented in participants CRFs, medical notes, and an AE log and will record the following information: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Only AEs that are judged to be related to the study intervention or procedures will be reported to the sponsor.

All SAEs will be reported by the investigators to the sponsor within 24 hours of discovery or notification and the report will be signed by the chief investigator within 7 days. If the SAE is deemed related to the research procedures or intervention and is unexpected, a report will be sent to the research ethics committee (REC) within 15 days.

Patient and public involvement

A patient and public involvement (PPI) group has been convened and will meet with the research team to review progress and address issues that arise throughout the duration of the study. The PPI partners will assist in the interpretation and dissemination of results. The trial was designed in consultation

with PPI partners who advised on intervention content and outcome measure acceptability, paying particular attention to patient burden, ensuring outcome measures would not over-burden participants. The PPI group approved the final design and duration of this intervention and advised the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise capability.

Changes to the study protocol following the COVID-19 pandemic

The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst patient safety remains the absolute priority of clinical and research teams, there is a need for research to continue in a safe way that balances the benefits of continuing programs of research against the risks from COVID-19. We have amended the study protocol in several ways to reduce any additional exposure of patients to clinical environments where COVID-19 may be present:

- We have reduced the number of study visits to a minimum. The original study flow diagram is included in Additional file 1. All interim assessments have been removed in the modified protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient clinical care. That is to say, when they attend for their baseline and follow-up study visits they will have their clinical review and clinical blood tests as they would for their normal clinical care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical environment over-and-above their normal care.
- The original study design included a 2-week face-to-face training period where participants would attend the hospital to learn how to complete the exercises and the exercise program with a member of the research team. This training period will now be done remotely, via video conferencing, with discussion and feedback over the telephone and using the instructional videos and literature that support the home-based exercise intervention.
- When participants attend for their study visits, departmental procedures have been updated to now include meticulous cleaning of all equipment before and after use, one-way flows of participants to ensure participants do not mix, and the use of personal protective equipment for all staff and participants.

The above changes have been agreed with the local REC and the study sponsor and have allowed recommencement of study recruitment and procedures.

DISCUSSION

This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare

utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR to evaluate the structural and functional changes of the heart in this at risk population.

Qualitative data will provide valuable personal perspectives on the acceptability of this specific exercise program. Transplant recipients experience complex medical journeys and are likely to have specific unmet needs in the area of exercise and lifestyle.[90] This will be valuable information for future randomised controlled trials (RCTs) and exercise guideline development.

Home-based intervention outcomes are reliant on accurate reporting by participants with regards to frequency, intensity, and duration of exercise performed. This under-reporting is often a limitation of unsupervised interventions. We will ensure participants are correctly advised of how to monitor and report their exercise completion throughout the trial and encourage this through telephone communications.

We anticipate that a positive outcome will lead to both an increased understanding of the specific exercise requirements of KTRs and the development of new programs that promote longer-term engendered lifestyle change that can be incorporated into standard practice with much lower financial implications than in-centre supervised rehabilitation.

ETHICS AND DISSEMINATION

Ethical issues

University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). The first participant was recruited on 09/03/2020. The predicted study end date is 31/12/2022. This manuscript is quorate with the most recent approved protocol (version 6 26.08.2020). Relevant parties will be informed of any substantial protocol modifications. Steps have been taken when designing this protocol to minimise the ethical implications and ensure patient welfare. The study will comply with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research Governance Framework for Health and Social Care.

Dissemination: On completion the results of this study will be published in peer-reviewed journals and presented at national and international conferences. Contributions of all authors to manuscripts arising from this study will be made explicit in the relevant of each individual journal. Participant level data will be available following publication of results on request to the Chief Investigator. Results will also be disseminated to the patient and public community via social media and newsletter articles and presentations at patient conferences and forums, led by the patient partners. It is anticipated that the results of this study will inform future design of larger RCTs in this subject area and contribute to future specific physical activity guidelines in this population.

Twitter: REB, @RBillany; MGB, @DrMattGB.

Author contributions: REB and MGB: study design, study setup, completion of study visits, drafting manuscript, revision of manuscript, finalising manuscript. NCB, TJW, ACW, SFA, KAR, KC, EMB, NJC, JB, GPM, JOB, and ACS: study design, drafting manuscript, revision of manuscript. NV, KP, JW: completion of study visits, drafting manuscript, revision of manuscript.

Funding: This study is funded by a project grant from Kidney Research UK (ref: KS_RP_003_20180913). Neither the sponsor nor the funder had or will have any input into study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Acknowledgements: This research is supported by the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests: None declared.

Consent for publication: Not applicable.

Figure Caption:

Figure 1. ECSERT study flow diagram

REFERENCES

1. Oniscu GC, Brown H, Forsythe JLR. How great is the survival advantage of transplantation over dialysis in elderly patients? *Nephrol Dial Transpl* 2004;19(4):945-51. doi: 10.1093/ndt/gfh022
2. Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. *Nephron* 2016;132 Suppl 1:111-44. doi: 10.1159/000444819
3. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. *World J Transplant* 2015;5(4):183-95. doi: 10.5500/wjt.v5.i4.183
4. UK Renal Registry (2020) UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from renal.org/audit-research/annual-report
5. Kasiske BL, Guijarro C, Massy ZA, et al. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996;7(1):158-65
6. Carpenter MA, John A, Weir MR, et al. BP, cardiovascular disease, and death in the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *J Am Soc Nephrol* 2014;25(7):1554-62. doi: 10.1681/asn.2013040435
7. Mall G, Huther W, Schneider J, et al. Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrol Dial Transplant* 1990;5(1):39-44. doi: 10.1093/ndt/5.1.39
8. Bakri RS, Afzali B, Covic A, et al. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. *Clin Transpl* 2004;18(2):201-04. doi: 10.1111/j.1399-0012.2004.00156.x
9. Liefeldt L, Budde K. Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int* 2010;23(12):1191-204. doi: 10.1111/j.1432-2277.2010.01159.x
10. Van Laecke S, Malfait T, Schepers E, et al. Cardiovascular disease after transplantation: an emerging role of the immune system. *Transpl Int* 2018;31(7):689-99. doi: 10.1111/tri.13160
11. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 2007;50(3):217-24. doi: 10.1016/j.jacc.2007.03.037
12. Aalten J, Peeters SA, van der Vlugt MJ, et al. Is standardized cardiac assessment of asymptomatic high-risk renal transplant candidates beneficial? *Nephrol Dial Transplant* 2011;26(9):3006-12. doi: 10.1093/ndt/gfq822
13. Mansell H, Rosaasen N, Dean J, et al. Evidence of enhanced systemic inflammation in stable kidney transplant recipients with low Framingham risk scores. *Clin Transpl* 2013;27(4):E391-E99
14. Mansell H, Stewart SA, Shoker A. Validity of cardiovascular risk prediction models in kidney transplant recipients. *Sci World J* 2014;2014:750579. doi: 10.1155/2014/750579
15. Devine PA, Courtney AE, Maxwell AP. Cardiovascular risk in renal transplant recipients. *J Nephrol* 2019;32(3):389-99. doi: 10.1007/s40620-018-0549-4
16. Kasiske BL. Epidemiology of cardiovascular disease after renal transplantation. *Transplantation* 2001;72(6 Suppl):S5-8. doi: 10.1097/00007890-200109271-00003
17. de Albuquerque Suassuna P, Sanders-Pinheiro H, de Paula R. Uremic Cardiomyopathy: A New Piece in the Chronic Kidney Disease-Mineral and Bone Disorder Puzzle. *Front Med (Lausanne)* 2018;5:206-06. doi: 10.3389/fmed.2018.00206
18. Aoki J, Ikari Y, Nakajima H, et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 2005;67(1):333-40. doi: 10.1111/j.1523-1755.2005.00086.x
19. Mark PB, Doyle A, Blyth KG, et al. Vascular function assessed with cardiovascular magnetic resonance predicts survival in patients with advanced chronic kidney disease. *J Cardiovasc Magn R* 2008;10:39. doi: 10.1186/1532-429x-10-39

20. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47(1):186-92. doi: 10.1038/ki.1995.22
21. Foley RN, Parfrey PS, Harnett JD, et al. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995;5(12):2024-31
22. Ali A, Macphee I, Kaski JC, et al. Cardiac and vascular changes with kidney transplantation. *Indian J Nephrol* 2016;26(1):1-9. doi: 10.4103/0971-4065.165003
23. Patel RK, Mark PB, Johnston N, et al. Renal Transplantation Is Not Associated with Regression of Left Ventricular Hypertrophy: A Magnetic Resonance Study. *Clin J Am Soc Nephrol* 2008;3(6):1807-11. doi: 10.2215/cjn.01400308
24. Graham-Brown MPM, Adenwalla SF, Lai FY, et al. The reproducibility of cardiac magnetic resonance imaging measures of aortic stiffness and their relationship to cardiac structure in prevalent haemodialysis patients. *Clin Kidney J* 2018;11(6):864-73. doi: 10.1093/ckj/sfy042
25. Graham-Brown MPM, Rutherford E, Levelt E, et al. Native T1 mapping: inter-study, inter-observer and inter-center reproducibility in hemodialysis patients. *J Cardiovasc Magn R* 2017;19(1) doi: 10.1186/s12968-017-0337-7
26. Graham-Brown MP, Gulsin GS, Parke K, et al. A comparison of the reproducibility of two cine-derived strain software programmes in disease states. *Eur J Radiol* 2019;113:51-58. doi: 10.1016/j.ejrad.2019.01.026
27. Kriska AM, Saremi A, Hanson RL, et al. Physical activity, obesity, and the incidence of type 2 diabetes in a high-risk population. *Am J Epidemiol* 2003;158(7):669-75. doi: 10.1093/aje/kwg191
28. Stamatakis E, Gale J, Bauman A, et al. Sitting Time, Physical Activity, and Risk of Mortality in Adults. *J Am Coll Cardiol* 2019;73(16):2062-72. doi: doi:10.1016/j.jacc.2019.02.031
29. Koolhaas CM, Dhana K, Schoufour JD, et al. Impact of physical activity on the association of overweight and obesity with cardiovascular disease: The Rotterdam Study. *Eur J Prev Cardiol* 2017;24(9):934-41. doi: 10.1177/2047487317693952
30. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J* 2013;77(2):281-92. doi: 10.1253/circj.cj-13-0007
31. Barengo NC, Hu G, Lakka TA, et al. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 2004;25(24):2204-11. doi: 10.1016/j.ehj.2004.10.009
32. Nielens H, Lejeune TM, Lalaoui A, et al. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. *Nephrol Dial Transpl* 2001;16(1):134-40. doi: 10.1093/ndt/16.1.134
33. Dontje ML, de Greef MH, Krijnen WP, et al. Longitudinal measurement of physical activity following kidney transplantation. *Clin Transplant* 2014;28(4):394-402. doi: 10.1111/ctr.12325
34. Masiero L, Puoti F, Bellis L, et al. Physical activity and renal function in the Italian kidney transplant population. *Ren Fail* 2020;42(1):1192-204. doi: 10.1080/0886022x.2020.1847723
35. Wilkinson TJ, Clarke AL, Nixon DGD, et al. Prevalence and correlates of physical activity across kidney disease stages: an observational multicentre study. *Nephrol Dial Transpl* 2019 doi: 10.1093/ndt/gfz235
36. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012;2(2):1143-211. doi: 10.1002/cphy.c110025
37. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. *J Appl Physiol* 2011;111(5):1497-504. doi: 10.1152/japplphysiol.00420.2011
38. Oguchi H, Tsujita M, Yazawa M, et al. The efficacy of exercise training in kidney transplant recipients: a meta-analysis and systematic review. *Clin Exp Nephrol* 2019;23(2):275-84. doi: 10.1007/s10157-018-1633-8

39. Mathur S, Janaudis-Ferreira T, Wickerson L, et al. Meeting Report: Consensus Recommendations for a Research Agenda in Exercise in Solid Organ Transplantation. *Am J Transplant* 2014;14(10):2235-45. doi: 10.1111/ajt.12874
40. Masajtis-Zagajewska A, Muras K, Nowicki M. Effects of a Structured Physical Activity Program on Habitual Physical Activity and Body Composition in Patients With Chronic Kidney Disease and in Kidney Transplant Recipients. *Exp Clin Transplant* 2019;17(2):155-64. doi: 10.6002/ect.2017.0305
41. O'Connor EM, Koufaki P, Mercer TH, et al. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients - A pilot randomised controlled trial. *PLoS One* 2017;12(2):e0171063. doi: 10.1371/journal.pone.0171063
42. Moraes Dias CJ, Anaisse Azoubel LM, Araujo Costa H, et al. Autonomic modulation analysis in active and sedentary kidney transplanted recipients. *Clin Exp Pharmacol Physiol* 2015;42(12):1239-44. doi: 10.1111/1440-1681.12481
43. Karelis AD, Hébert MJ, Rabasa-Lhoret R, et al. Impact of Resistance Training on Factors Involved in the Development of New-Onset Diabetes After Transplantation in Renal Transplant Recipients: An Open Randomized Pilot Study. *Can J Diabetes* 2016;40(5):382-88. doi: 10.1016/j.jcjd.2015.08.014
44. Roi GS, Stefoni S, Mosconi G, et al. Physical activity in solid organ transplant recipients: organizational aspects and preliminary results of the Italian project. *Transplant Proc* 2014;46(7):2345-9. doi: 10.1016/j.transproceed.2014.07.055
45. Romano G, Simonella R, Falleti E, et al. Physical training effects in renal transplant recipients. *Clin Transplant* 2010;24(4):510-4. doi: 10.1111/j.1399-0012.2009.01098.x
46. Kinnafick FE, Thogersen-Ntoumani C, Shepherd SO, et al. In It Together: A Qualitative Evaluation of Participant Experiences of a 10-Week, Group-Based, Workplace HIIT Program for Insufficiently Active Adults. *J Sport Exerc Psychol* 2018;40(1):10-19. doi: 10.1123/jsep.2017-0306
47. van Baar ME, Dekker J, Oostendorp RA, et al. Effectiveness of exercise in patients with osteoarthritis of hip or knee: nine months' follow up. *Ann Rheum Dis* 2001;60(12):1123-30. doi: 10.1136/ard.60.12.1123
48. Timmons JF, Griffin C, Cogan KE, et al. Exercise Maintenance in Older Adults 1 Year After Completion of a Supervised Training Intervention. *J Am Geriatr Soc* 2020;68(1):163-69. doi: 10.1111/jgs.16209
49. Hibbard JH, Greene J. What The Evidence Shows About Patient Activation: Better Health Outcomes And Care Experiences; Fewer Data On Costs. *Health Affairs* 2013;32(2):207-14. doi: 10.1377/hlthaff.2012.1061
50. Skolasky RL, Mackenzie EJ, Wegener ST, et al. Patient activation and adherence to physical therapy in persons undergoing spine surgery. *Spine (Phila Pa 1976)* 2008;33(21):E784-E91. doi: 10.1097/BRS.0b013e31818027f1
51. Baggetta R, D'Arrigo G, Torino C, et al. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: a secondary analysis of the EXCITE trial. *BMC Geriatr* 2018;18(1):248. doi: 10.1186/s12877-018-0938-5
52. Imran HM, Baig M, Erqou S, et al. Home-Based Cardiac Rehabilitation Alone and Hybrid With Center-Based Cardiac Rehabilitation in Heart Failure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019;8(16):e012779. doi:10.1161/JAHA.119.012779
53. Uchiyama K, Washida N, Morimoto K, et al. Home-based Aerobic Exercise and Resistance Training in Peritoneal Dialysis Patients: A Randomized Controlled Trial. *Sci Rep* 2019;9(1):2632. doi: 10.1038/s41598-019-39074-9
54. Aoike DT, Baria F, Kamimura MA, et al. Home-based versus center-based aerobic exercise on cardiopulmonary performance, physical function, quality of life and quality of sleep of overweight patients with chronic kidney disease. *Clin Exp Nephrol* 2018;22(1):87-98. doi: 10.1007/s10157-017-1429-2

55. Majchrzak KM, Pupim LB, Chen K, et al. Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days. *J Ren Nutr* 2005;15(2):217-24. doi: 10.1053/j.jrn.2004.08.002
56. Carvalho EV, Reboredo MM, Gomes EP, et al. Physical activity in daily life assessed by an accelerometer in kidney transplant recipients and hemodialysis patients. *Transplant Proc* 2014;46(6):1713-7. doi: 10.1016/j.transproceed.2014.05.019
57. Borg GA. Perceived exertion: a note on "history" and methods. *Med Sci Sports* 1973;5(2):90-3.
58. Brzycki M. Strength Testing—Predicting a One-Rep Max from Reps-to-Fatigue. *Journal of Physical Education, Recreation & Dance* 1993;64(1):88-90. doi: 10.1080/07303084.1993.10606684
59. Schoenfeld BJ, Grgic J, Ogborn D, et al. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-analysis. *J Strength Cond Res* 2017;31(12):3508-23. doi: 10.1519/jsc.0000000000002200
60. Hunold P, Vogt FM, Heemann UW, et al. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI--study in dialysis patients examined before and after dialysis. *J Cardiovasc Magn R* 2003;5(4):553-61. doi: 10.1081/jcmr-120025230
61. Graham-Brown MP, March DS, Churchward DR, et al. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016;90(4):835-44. doi: 10.1016/j.kint.2016.07.014
62. Xu HY, Yang ZG, Zhang Y, et al. Prognostic value of heart failure in hemodialysis-dependent end-stage renal disease patients with myocardial fibrosis quantification by extracellular volume on cardiac magnetic resonance imaging. *BMC Cardiovasc Disord* 2020;20(1):12. doi: 10.1186/s12872-019-01313-2
63. Graham-Brown MP, Singh AS, Gulsin GS, et al. Defining myocardial fibrosis in haemodialysis patients with non-contrast cardiac magnetic resonance. *BMC Cardiovasc Disord* 2018;18(1):145. doi: 10.1186/s12872-018-0885-2
64. Xue H, Brown LAE, Nielles-Vallespin S, et al. Automatic in-line quantitative myocardial perfusion mapping: Processing algorithm and implementation. *Magn Reson Med* 2020;83(2):712-30. doi: 10.1002/mrm.27954
65. Gould DW, Watson EL, Wilkinson TJ, et al. Ultrasound assessment of muscle mass in response to exercise training in chronic kidney disease: a comparison with MRI. *J Cachexia Sarcopenia Muscle* 2019;10(4):748-55. doi: 10.1002/jcsm.12429
66. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Resp Crit Care* 2003;167(2):211-77. doi: 10.1164/rccm.167.2.211
67. Feiring DC, Ellenbecker TS, Derscheid GL. Test-Retest Reliability of the Biodex Isokinetic Dynamometer. *J Orthop Sport Phys* 1990;11(7):298-300. doi: 10.2519/jospt.1990.11.7.298
68. Wilkinson TJP, Xenophontos SM, Gould DWP, et al. Test-retest reliability, validation, and "minimal detectable change" scores for frequently reported tests of objective physical function in patients with non-dialysis chronic kidney disease. *Physiother Theory Pract* 2019;35(6):565-76. doi: 10.1080/09593985.2018.1455249
69. Wilkinson TJ, Gabrys I, Lightfoot CJ, et al. A Systematic Review of Handgrip Strength Measurement in Clinical and Epidemiological Studies of Kidney Disease: Toward a Standardized Approach. *J Ren Nutr* 2021 doi: 10.1053/j.jrn.2021.06.005
70. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x
71. Hadjiioannou I, Wong K, Lindup H, et al. Test-restest reliability for physical function measures in patients with chronic kidney disease. *J Ren Care* 2019 doi: 10.1111/jorc.12310
72. Wilkinson TJ, Nixon DGD, Smith AC. Postural stability during standing and its association with physical and cognitive functions in non-dialysis chronic kidney disease patients. *Int J Nephrol Urol* 2019;51(8):1407-14. doi: 10.1007/s11255-019-02192-4
73. Eston RG, Reilly T. Kinanthropometry and exercise physiology laboratory manual: tests, procedures, and data. 3rd ed. Abingdon: Routledge 2009.

74. Chertow GM, Lowrie EG, Wilmore DW, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995;6(1):75-81.
75. Macdonald JH, Marcora SM, Jibani M, et al. Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transpl* 2006;21(12):3481-7. doi: 10.1093/ndt/gfl432
76. Raj R, Ahuja K, Frandsen M, et al. Validation of the IPOS-Renal Symptom Survey in Advanced Kidney Disease: A Cross-sectional Study. *J Pain Symptom Manage* 2018;56(2):281-87. doi: 10.1016/j.jpainsymman.2018.04.006
77. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996:220-33.
78. Wang S-Y, Zang X-Y, Liu J-D, et al. Psychometric Properties of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) in Chinese Patients Receiving Maintenance Dialysis. *J Pain Symptom Manage* 2015;49(1):135-43. doi: 10.1016/j.jpainsymman.2014.04.011
79. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13(2):63-74. doi: 10.1016/s0885-3924(96)00274-6
80. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4
81. Hibbard JH, Stockard J, Mahoney ER, et al. Development of the Patient Activation Measure (PAM): Conceptualizing and Measuring Activation in Patients and Consumers. *Health Serv Res* 2004;39(4p1):1005-26. doi: 10.1111/j.1475-6773.2004.00269.x
82. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med* 2004;36(8):588-94
83. Cavanaugh KL, Osborn CY, Tentori F, et al. Performance of a brief survey to assess health literacy in patients receiving hemodialysis. *Clinical Kidney Journal* 2015;8(4):462-8. doi: https://dx.doi.org/10.1093/ckj/sfv037
84. Dageforde LA, Cavanaugh KL, Moore DE, et al. Validation of the written administration of the short literacy survey. *J Health Commun* 2015;20(7):835-42. doi: 10.1080/10810730.2015.1018572
85. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790
86. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64(10):651-4. doi: 10.1016/0002-9149(89)90496-7
87. Dillon CB, Fitzgerald AP, Kearney PM, et al. Number of Days Required to Estimate Habitual Activity Using Wrist-Worn GENEActiv Accelerometer: A Cross-Sectional Study. *PLOS ONE* 2016;11(5):e0109913. doi: 10.1371/journal.pone.0109913
88. Moore CG, Carter RE, Nietert PJ, et al. Recommendations for Planning Pilot Studies in Clinical and Translational Research. *J Clin Transl Sci* 2011;4(5):332-37. doi: 10.1111/j.1752-8062.2011.00347.x
89. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65(3):301-8. doi: 10.1016/j.jclinepi.2011.07.011
90. Gordon EJ, Prohaska T, Siminoff LA, et al. Needed: Tailored exercise regimens for kidney transplant recipients. *Am J Kidney Dis* 2005;45(4):769-74. doi: 10.1053/j.ajkd.2005.01.002

Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
RTRs	

• Prevalent KTR >1 year
• Male or female, aged >18 years old
• Willing and able to give informed consent for participation in the study
• Increased cardiometabolic risk with at least one of:
  • Diabetes mellitus
  • Dyslipidaemia
  • Hypertension
  • Obesity (BMI >30)
  • History of ischaemic heart disease/cerebrovascular disease
	• Inability to give informed consent or comply with testing and exercise protocol for any reason
	• Unable to undergo CMR scanning (incompatible implants, claustrophobia, allergy to agents etc.)
	• Female participants who are pregnant, lactating, or planning pregnancy during the course of the study
	• Scheduled elective surgery or other procedures requiring general anaesthesia during the study
	• Any other significant disease or disorder*

Healthy controls	

• Age <18 years
• No documented history of major cardiorespiratory chronic condition
• None of the following cardiometabolic risk factors:
  • Diabetes mellitus
  • Dyslipidaemia
  • Hypertension
  • History of ischaemic heart disease/cerebrovascular disease
  • Obesity (BMI>30)
• Not on any medication
	• Unable to undertake exercise testing due to physical or psychological barriers
	• Scheduled elective surgery or other procedures requiring general anaesthesia during the study
	• Inability to give informed consent or comply with testing and exercise protocol for any reason
	• Any other significant disease or disorder*

*i.e. significant co-morbidity including unstable hypertension, potentially lethal arrhythmia, myocardial infarction within 6 months, unstable angina, active liver disease, uncontrolled diabetes mellitus (HbA1c ≥ 9%), advanced cerebral or peripheral vascular disease which, in the opinion of the patient's own clinician, may either put the patient at risk because of participation in the study, or may influence the result of the study, or the patient's ability to participate in the study.

Additional file details

File name: Additional File 1

File format: Additional File 1.pdf

Title of data: Original ECSERT flow diagram (pre-COVID-19)

Description of data: Flow diagram prior to COVID-19 amendments

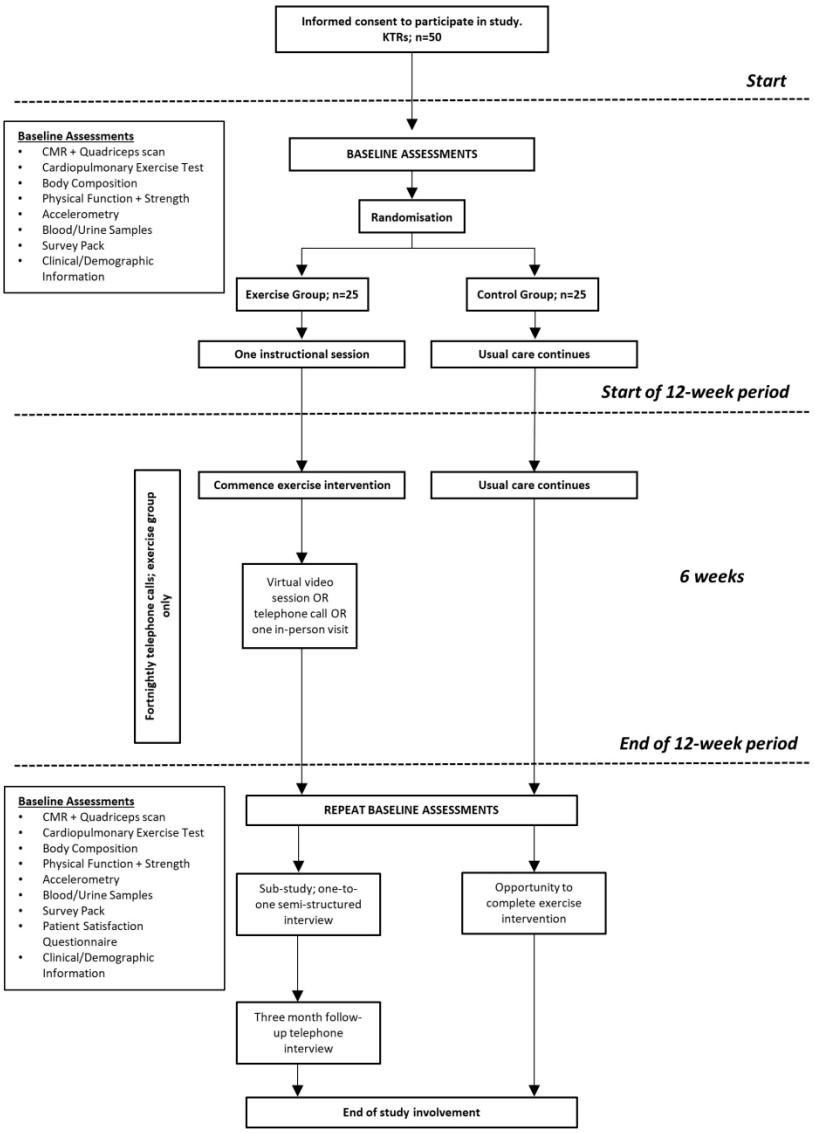

Figure 1 ECSERT Study Flow Diagram

170x219mm (300 x 300 DPI)

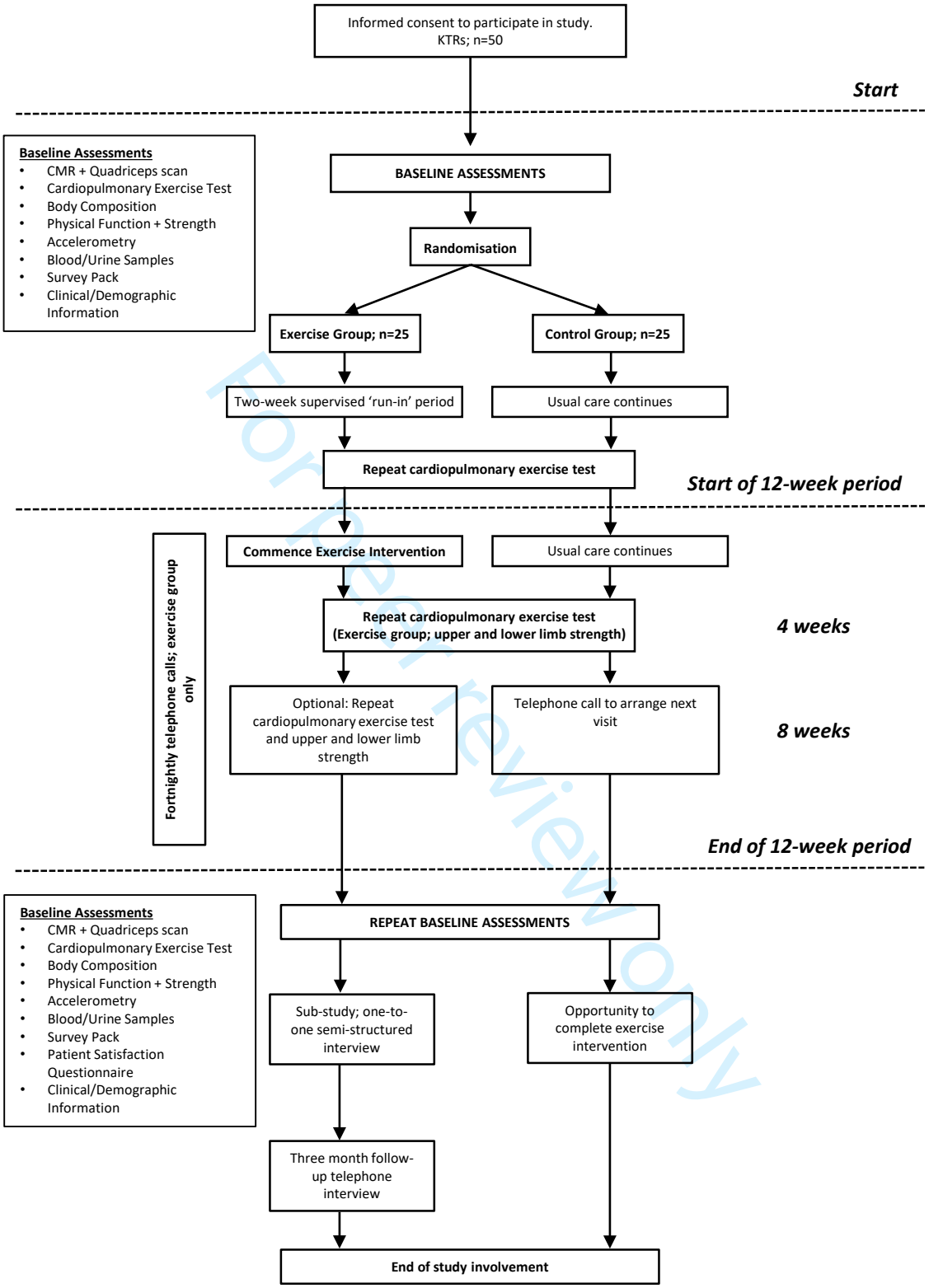

Figure X. Original ECSERT study flow diagram (pre-COVID-19)

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1, lines 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 2, lines 67)
	2b	All items from the World Health Organization Trial Registration Data Set (Yes, throughout)
Protocol version	3	Date and version identifier (page 16, line 494)
Funding	4	Sources and types of financial, material, and other support (page 16, line 506 and page 16, lines 511-513)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (page 1 and 15)
	5b	Name and contact information for the trial sponsor (page 16, line 488)
	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 (page 16, 506-509)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) N/A
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Introduction, page 3)
	6b	Explanation for choice of comparators (Introduction, page 3)
Objectives	7	Specific objectives or hypotheses (Page 4)

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) (Page 5)
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 (Page 5, line 141-143)
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) (Table 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 5 and 6)
	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) (Page 6, lines 176-178)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 10, lines 323-327)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 5, line 164)
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 (Study timeline, page 7)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 11, lines 346-348)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 5, 140+)
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 (Page 5, 154-159)
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 (Page 5, 154-159)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Page 5, 158)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A

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 (Page 7-11)
	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 (Page 11)
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 (Page 11, lines 349-354)
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 (Page 11 and 12)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A

	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) (Page 12)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC) or Data and Safety Monitoring Board (DCMB); 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 A DSMB is indicated, from a practical perspective in the following circumstances: 1. If the trial is intended to provide definitive information about effectiveness and/or safety of a medical or bio-behavioral intervention 2. If there are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity 3. If the trial is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications 4. If it would ethically be important for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed The ECSERT study does not meet any of these criteria as a pilot/feasibility study
	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 N/A
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 (Page 12, safety reporting)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A aside from usual sponsor audits
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 16, ethical issues)
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) (Page 16, ethical issues)

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (consent form)
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 (Page 11)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 16, line 515)
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 (Page 17, availability of data)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 17, availability of data)
	31b	Authorship eligibility guidelines and any intended use of professional writers (Page 17, availability of data)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 17, availability of data)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Yes
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 (Page 10)

*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.