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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

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Complete List of Authors:	<p>Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences</p> <p>Wilkinson, Thomas ; University of Leicester, Department of Health Sciences</p> <p>Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences</p> <p>Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Brady, Emer; University of Leicester, Department of Cardiovascular Sciences</p> <p>Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Cooper, Nicola; University of Leicester, Department of Health Sciences</p> <p>Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research</p> <p>Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences</p> <p>Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Smith, Alice; University of Leicester, Department of Health Sciences</p> <p>Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p>

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3 1 **A pilot randomised controlled trial of a structured, home-based exercise program on**
4 **cardiovascular structure and function in kidney transplant recipients: The ECSERT study**
5 **design and methods**
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10 Roseanne E Billany^{1,2}, Noemi Vadaszy³, Nicolette C Bishop⁴, Thomas J Wilkinson³, Sherna Adenwalla^{1,2},
11 Katherine A Robinson¹, Kathryn Croker², Emer M Brady¹, Joanne Wormleighton⁵, Kelly Parke^{1,5}, Nicola
12 J Cooper³, Angela C Webster⁶, Jonathan Barratt^{1,2}, Gerry P McCann¹, James O Burton^{1,2,5}, Alice C Smith³,
13 Matthew PM Graham-Brown^{1,2}
14
15
16

17
18
19 ¹ Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

20 ² John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

21 ³ Department of Health Sciences, University of Leicester, Leicester, UK

22 ⁴ School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

23 ⁵ Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK

24 ⁶ Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and
25 Transplant Research, Westmead Hospital, Sydney, NSW, Australia.
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27
28
29
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33

34 **Corresponding author:**

35 Dr Matthew Graham-Brown

36 Department of Cardiovascular Sciences

37 University of Leicester

38 Leicester

39 United Kingdom

40 mgb23@leicester.ac.uk
41
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3 35 **ABSTRACT**
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6 37 **Background:** Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney
7
8 38 transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by
9
10 39 clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes
11
12 40 in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population,
13
14 41 evidence is limited, and physical activity levels and patient activation towards exercise and self-
15
16 42 management are low. This pilot study will assess the feasibility of delivering a structured, home-based
17
18 43 exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the
19
20 44 putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality
21
22 45 of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise
23
24 46 program.
25

26 47
27 48 **Methods and analysis:** Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-
28
29 49 based combined resistance and aerobic exercise intervention or; (2) the control; usual care.
30
31 50 Intervention participants will have one introductory session for instruction and practice of the
32
33 51 recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access
34
35 52 to instructional videos. Outcomes, to be assessed prior to randomisation and post-intervention,
36
37 53 include: cardiac structure and function with stress-perfusion cardiac magnetic resonance imaging,
38
39 54 cardiorespiratory fitness, physical function, blood biomarkers of cardiometabolic health, quality of life,
40
41 55 and patient activation. The study will also evaluate the feasibility of recruitment, randomisation,
42
43 56 retention, assessment procedures, and the intervention implementation. These data will be used to
44
45 57 inform the power calculations for future definitive trials.
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47 58

48 59 **Ethics and dissemination:** The protocol was reviewed and given favourable opinion by the East
49
50 60 Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be
51
52 61 published in peer-reviewed academic journals and will be disseminated to the patient and public
53
54 62 community via social media, newsletter articles, and presentations at conferences.
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56 63

57 64 **Trial registration number:** NCT04123951; prospectively registered.
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3 67 **ARTICLE SUMMARY**

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5 68 **Strengths and limitations of this study:**

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- 7
8 70 • Data on the effects of exercise interventions on the cardiac structural and functional aspects
9 71 of CVD in this population are lacking and baseline values of multiparametric cardiac magnetic
10 72 resonance imaging in KTRs are previously undefined.
11
12
13 73 • This study uses a novel home-based exercise intervention with the potential to translate into
14 74 a widespread, low-resource intervention compared to in-centre, supervised interventions
15 75 that are costly and labour intensive.
16
17
18 76 • As it can be difficult to ensure control groups are not influenced to change their lifestyle as a
19 77 result of being part of the study; control participants will be offered the intervention after
20 78 completion of the study.
21
22
23 79 • This study will provide quantitative and qualitative feasibility and pilot data to inform a
24 80 definitive randomised controlled trial that will explore longer-term engendered lifestyle
25 81 change in this population in response to a complex, home-based, lifestyle intervention.
26
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28 82 • Secondary outcome analysis will identify the putative cardiometabolic and muscular effects
29 83 of the intervention, although these results would need confirming in adequately powered
30 84 studies due to the small sample size of this pilot study.
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86 BACKGROUND

87 Kidney transplantation is the preferred modality of renal replacement therapy for patients with end
88 stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage
89 over remaining on dialysis, cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and
90 graft loss.¹⁻³ Since 2015, mortality rates attributed to CVD have been rising.³ Cardiovascular disease in
91 kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,^{2,4,5} which
92 drive classical atheromatous coronary artery disease, and non-traditional risk factors which drive
93 pathological changes in cardiovascular structure and function that associate with mortality.⁶
94 Immunosuppressive agents are well known to drive traditional CVD risk factors,² but also drive non-
95 traditional cardiometabolic risk factors.^{7,8} Non-traditional cardiometabolic risk factors, including
96 endothelial dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-
97 mineral metabolism,⁹⁻¹¹ are of at least equal importance in the pathogenesis of CVD in KTRs.⁶ This is
98 further illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate
99 cardiovascular risk in patients with chronic kidney disease (CKD);¹⁰ coronary revascularisation does
100 not improve outcomes for KTRs as it does in the general population¹¹ and cardiac events are more
101 likely to be fatal in KTRs.¹²

102 Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”,
103 is characterised by stereotypical changes in the cardiovascular structure and function of the heart such
104 as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,¹³
105 myocardial fibrosis,¹⁴ and aortic stiffness¹⁵; all of which relate to poor cardiovascular outcomes.^{16,17}
106 Although structural and functional improvements of the heart and vessels have been seen post-
107 transplantation in some studies,¹⁸ others have shown no regression¹⁹ and parameters such as LVH are
108 independent factors for cardiac failure and mortality in KTRs.²⁰ Cardiac magnetic resonance imaging
109 (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown
110 methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic
111 function to be reproducible in patients with kidney disease,²¹⁻²³ making CMR the ideal imaging
112 modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.
113 Numerous epidemiological studies have observed the association between low levels of physical
114 activity and increased prevalence of CVD risk factors,²⁴⁻²⁶ and an inverse relationship between physical
115 activity and all-cause and CVD mortality.^{27,28} Physical activity levels in KTRs are lower than the general
116 population,^{29,30} with only 27% classified as meeting national recommended physical activity levels.³¹
117 Whilst physical activity levels improve in the year following transplantation, they plateau after one-
118 year.³⁰ In the general population, lifestyle changes that increase physical activity through structured
119 exercise lower mortality.^{32,33} Despite this evidence, there is a lack of rigorous research into the role of

1
2
3 120 increased physical activity in mitigating cardiovascular risk in KTRs.³⁴ Recent consensus
4 121 recommendations from experts and stakeholders highlighted the need for a priority research agenda
5 122 in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this
6 123 patient population.³⁵ Whilst supervised exercise interventions in KTRs improve cardiorespiratory
7 124 fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic
8 125 profile,³⁶⁻³⁸ vascular stiffening,³⁷ weight,³⁹ and inflammation,⁴⁰ they are not realistically deliverable in
9 126 the current financial climate and have not translated to clinical practice. Furthermore, exercise habits
10 127 following in-centre supervised programs are not maintained⁴¹⁻⁴³ which can be potentially attributed
11 128 to low levels of patient activation (a measure of a person's skills, confidence, and knowledge to
12 129 manage their own health) and a failure for such programs to engender sustained lifestyle changes.⁴⁴
13 130 ⁴⁵ Home-based exercise training programs have been shown to be deliverable in patients on dialysis
14 131 and patients undergoing cardiac rehabilitation,^{46 47} but the effectiveness and deliverability of home-
15 132 based exercise interventions are untested in KTRs. It cannot be assumed that such programs will be
16 133 acceptable to KTRs, whose home-lives, social and occupational circumstances are significantly
17 134 different to dialysis and cardiac patients. Many KTRs have had enforced sedentary lifestyles prior to
18 135 transplantation as dialysis patients and their goals for rehabilitation as well as the disease processes
19 136 at work may be different.

137 **Objectives**

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

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

148 Two sub-studies will assess:

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

152

153 **METHODS AND ANALYSIS**

154 **ECSERT trial design**

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

157 **Participant identification and recruitment**

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

168 **Randomisation**

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

175 **Intervention and comparator arms**

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

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

180 *Aerobic component*

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

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

186 *Resistance component*

187 The resistance component of the exercise intervention will include a combination of 6-8 exercises per
188 session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper
189 and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool
190 of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row,
191 reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has
192 modifications for different abilities and may be pragmatically adjusted or changed throughout the
193 study as required. These exercises were chosen based on their ability to be modified, their subjective
194 difficulty, and their safety when being performed by participants new to exercise in an unsupervised
195 environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on
196 consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of
197 10 repetitions (at 60% 1 repetition maximum (RM)), gradually increasing to 3-6 sets of 10 repetitions
198 over the study period with a minimum of 30 sec rest between sets. These figures may be adjusted to
199 accommodate different abilities and different rates of progression.

200 Participants will be provided with an exercise diary which includes additional instructions, dumbbells
201 and resistance bands, and access to educational and instructional videos. Instructional videos will
202 include: the importance of an active and healthy lifestyle, the importance of warming up and cooling
203 down and how to do it, a reminder of how to use the RPE scale, demonstrations of each resistance
204 exercise, and information about the aerobic component (videos can be viewed here:
205 https://www.youtube.com/playlist?list=PLwbE3AF9Ej_VuI5uoiF-C9Cl8wrgKz5Nv). Participants will
206 receive a telephone call from a member of the research team every two weeks in order to discuss
207 progression of the exercise and address any issues that may arise.

208 Control group: 'Usual care'

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

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2
3 216 assessments, they will be offered the opportunity to complete the same intervention as the exercise
4
5 217 group.

6 7 218 **Study timeline**

8 9 219 *Baseline assessments*

10
11 220 The ECSERT study timeline is shown in Figure 1. Baseline assessments will be carried out on the same
12
13 221 day and in conjunction with routine clinical appointments to prevent additional travel.

14 15 222 *Collection of routine clinical information and cost-effectiveness*

16
17 223 Clinical information will be extracted from the medical notes including: age, gender, ethnicity, primary
18
19 224 cause of kidney failure, transplant type, transplant vintage, dialysis duration, comorbidities,
20
21 225 blood/urine results, current medication, and smoking habits. This information will be used to primarily
22
23 226 capture confounding variables and during analyses of differences and similarities between groups.

24
25 227 A questionnaire will be administered at baseline to capture the previous 3 months of self-reported
26
27 228 healthcare utilisation including: inpatient and outpatient appointments, emergency care, community
28
29 229 and primary care services, support services, and changes in medications. This will be compared to data
30
31 230 gathered from healthcare records allowing validation of the questionnaire for future cost-
32
33 231 effectiveness analyses.

34 35 232 *Cardiac stress MRI*

36
37 233 All participants will undergo a comprehensive adenosine-stress perfusion CMR scans at baseline and
38
39 234 on study-completion. Participants will be scanned on a 3T platform (Skyra, Siemens Medical Imaging,
40
41 235 Erlangen, Germany) with an 18-channel phased-array receiver coil. New-generation gadolinium-based
42
43 236 contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m² will be given for
44
45 237 perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m² will undergo
46
47 238 non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

- 48 239 • Left and right-ventricular structure and function (left ventricular mass, left and right
49
50 240 ventricular volumes and ejection fractions);⁴⁹
- 51 241 • Tissue-characterisation with native and post-contrast T1 mapping and delayed gadolinium
52
53 242 enhancement;⁵⁰⁻⁵²
- 54 243 • Myocardial systolic-strain and peak early-diastolic strain rate;²³
- 55 244 • Quantitative perfusion imaging (coronary blood-flow to quantify coronary reserve and
56
57 245 ischaemia);⁵³
- 58 246 • Aortic distensibility.²¹

59 60 247 *Quadriceps MRI*

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

250 *Cardiopulmonary exercise test*

251 A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked
252 cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W)
253 every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min⁵⁵. Participants will be
254 encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured
255 (VO_2peak) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true
256 maximal (plateau) VO_2 (VO_2max) is less commonly achieved in deconditioned and/or clinical patients.
257 The test will be in the presence of a cardiac nurse to confirm safety to commence exercise training. A
258 non-invasive monitor (Moxy, Fortiori Design LLC., Minnesota, USA) will be worn on the quadriceps
259 muscle which uses near infrared spectroscopy (NIRS) to measure local oxygen saturation (SmO_2) and
260 total haemoglobin (THb) of the muscle.

261 *Lower limb Strength and muscular endurance*

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

268 *Handgrip strength*

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

272 *Gait speed*

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

276 *Functional mobility*

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

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2
3 280 *Balance and postural stability*
4

5 281 Postural stability and balance will be assessed using a previously reported method⁵⁸ with a FysioMeter
6 282 device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to
7
8 283 software on a portable computer (FysioMeter ApS, Brønderslev, Denmark).

9
10
11 284 *Quadriceps ultrasound and myotonometry*
12

13 285 Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D
14 286 ultrasonography (Clarius C3 HD Scanner, Clarius, Burnaby BC, Canada; 6 MHz) under resting conditions
15
16 287 with the participant lying prone at a 45° as previously described.⁵⁴ Rectus femoris and vastus lateralis
17 288 thickness, subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of
18
19 289 the viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be
20
21 290 obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

22
23
24 291 *Anthropometric measures*
25

26 292 Anthropometric measures of height, body mass, and waist and hip circumference will be attained in
27
28 293 accordance with standard protocols.⁵⁹ Bioelectrical impedance analysis (BIA) performed on an InBody
29 294 analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat
30
31 295 percentage, fat-free mass) and is validated for use in patients with CKD.^{60 61}

32
33 296 *Survey pack*
34

35 297 Participants will be provided with a survey pack containing the following questionnaires:

- 36
37 298 (1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the
38 299 presence and severity of disease related symptoms. The I-POS-Renal was developed based on
39
40 300 the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms
41
42 301 common in CKD such as pruritus and restless legs.⁶²
- 43
44 302 (2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess
45
46 303 generic health outcomes from the patient's perspective.⁶³
- 47
48 304 (3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item
49 305 multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert
50
51 306 scale that covers physical fatigue, functional fatigue, emotional fatigue, and social
52
53 307 consequences of fatigue with excellent internal consistency and test-retest reliability.^{64 65}
- 54
55 308 (4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality
56
57 309 and disturbances over a 1-month time interval.⁶⁶
- 58
59 310 (5) Patient Activation Measure (PAM): a validated, licenced tool that has been extensively tested
60 311 with reviewed findings from a large number of studies. It measures the spectrum of

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

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

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

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

323 *Habitual physical activity*

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

326 *Blood and urine sampling*

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

- 329 • Circulating markers of cardiovascular disease
- 330 • Circulating markers of systemic inflammation and oxidative stress
- 331 • Blood glucose and HbA1c
- 332 • Lipids and triglycerides
- 333 • Full blood count and renal profile

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

335 **Follow-up assessments**

336 Follow up visits are summarised in Figure 1. An instructional session (or more if required) following
337 baseline assessments will allow the intervention group to become familiar with the exercise
338 requirements and allow the research team to ensure safety and competence before commencing the
339 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-
340 week period for the intervention group only, participants will be invited to review exercise progression
341 (via video call or in-person), particularly if participants are struggling to undertake the requisite
342 amount of exercise, and as a refresher of the intervention. This combined with regular contact from
343 research staff should aid participant compliance and monitoring.

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3 344 Final assessments will be conducted for the exercise and control groups within 7 days of completing
4
5 345 the 12-week exercise or control period. Assessments completed will be identical to the baseline visit
6
7 346 with the addition of a 'patient satisfaction questionnaire' to allow pragmatic development of the
8
9 347 study. This will also be offered to participants who withdraw from the trial. Three months after
10
11 348 completing the exercise intervention, participants will be contacted for a semi-structured one-to-one
12
13 349 telephone interview. This will aim to understand the impact of the intervention, if any, on subsequent
14
15 350 lifestyle and exercise habits.

15 351 **Sub-studies**

16
17 352 Additional informed consent will be sought for:

- 18
19 353 1. Ten 'healthy' control participants to undertake a CPET to assess the differences, if any,
20
21 354 between CPET parameters in 'healthy controls' versus KTRs, particularly during the recovery
22
23 355 period.
- 24
25 356 2. KTRs completing the exercise intervention will be invited to undertake a semi-structured
26
27 357 interview (via telephone, video call, or in-person) incorporating exercise self-efficacy,
28
29 358 enjoyment, difficulties encountered, perceived advantages and disadvantages of the
30
31 359 intervention, and study design. Participants who withdraw before the end of the intervention
32
33 360 will also be invited to attend, although in line with ethical standards, this will be optional.

34 361 **Sample size**

35
36 362 The purpose of this pilot study is to obtain appropriate data to adequately power future definitive
37
38 363 trials;⁷⁴ a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on
39
40 364 accepted values to provide adequate estimates of standard deviations for future power calculations.⁷⁵

41 365 **Data collection and management**

42
43 366 Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will
44
45 367 be entered into a secure database and will only be accessible on password-protected computers at
46
47 368 UHL and University of Leicester by relevant members of the study team. No identifying information
48
49 369 will be kept in electronic form. All source data and original participant identities will be kept in a locked
50
51 370 office in the trial site file only at UHL.

52 371 **Data analysis**

53
54 372 Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous
55
56 373 data to be expressed as mean (\pm standard deviation), if normally distributed or median (interquartile
57
58 374 range) if not. To investigate the differences between interventions we will use analysis of (co-)
59
60 375 variance. Independent samples t-tests and Mann-Whitney U tests will be used assess for baseline

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3 376 differences between variables for normally and non-normally distributed data respectively. These
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5 377 data will be used to inform the power calculation for future definitive trials.

6
7 378 Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive
8
9 379 thematic analysis to explore themes emerging from patient journeys through, and experiences of, the
10
11 380 interventions and outcome measures.

12
13 381 Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

- 14
15 382 • *Eligibility*: the percentage of patients screened who are eligible.
16
17 383 • *Recruitment rate*: the percentage of patients eligible who consent to the trial and the monthly
18 384 recruitment rate.
19
20 385 • *Adherence to the exercise intervention*: the number of completed sessions per week and
21 386 specific intensity and durations achieved.
22
23 387 • *Acceptability of randomisation*: comparison of the final group characteristics and
24 388 identification of any stratification variables, if applicable.
25
26 389 • *Attrition rate*: the number of participants that drop-out of the study.
27
28 390 • *Outcome acceptability*: the percentage of missing data for each outcome measure.
29
30 391 • *Safety*: The number of self-reported injuries or adverse events throughout the trial.

31
32 392 The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility ($\geq 50\%$),
33 393 recruitment success of 20% of eligible participants (≥ 2 participants per month), adherence (an average
34 394 of 3 exercise sessions per week) and attrition ($\leq 30\%$).

35 36 37 38 395 **Safety reporting**

39
40 396 All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) or serious
41 397 adverse reactions (SARs) will be recorded from the time a patient enters the study to the final study
42 398 visit. Each AE or AR will be considered for severity, causality, and expectedness and may be reclassified
43 399 as an SAE or SAR if required.

44
45
46
47 400 An SAE is any AE that:

- 48
49 401 • is life threatening
50 402 • requires hospitalization or prolongation of a hospital admission
51 403 • results in a persistent or significant disability/incapacity
52 404 • is a congenital anomaly
53 405 • results in death

54
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57 406 All AEs and ARs will be documented in participants CRFs, medical notes, and an AE log and will record
58 407 the following information: description, date of onset and end date, severity, assessment of
59
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3 408 relatedness to study, other suspect device and action taken. Only AEs that are judged to be related to
4
5 409 the study intervention or procedures will be reported to the sponsor.

6 410 All SAEs will be reported by the investigators to the sponsor within 24 hours of discovery or notification
7
8 411 and the report will be signed by the chief investigator within 7 days. If the SAE is deemed related to
9
10 412 the research procedures or intervention and is unexpected, a report will be sent to the research ethics
11
12 413 committee (REC) within 15 days.

13 414 **Patient and public involvement**

15 415 A patient and public involvement (PPI) group has been convened and will meet with the research team
16
17 416 to review progress and address issues that arise throughout the duration of the study. The PPI partners
18
19 417 will assist in the interpretation and dissemination of results. The trial was designed in consultation
20
21 418 with PPI partners who advised on intervention content and outcome measure acceptability, paying
22
23 419 particular attention to patient burden, ensuring outcome measures would not over-burden
24
25 420 participants. The PPI group approved the final design and duration of this intervention and advised
26
27 421 the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise
28
29 422 capability.

30 423 **Changes to the study protocol following the COVID-19 pandemic**

31 424 The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst
32
33 425 patient safety remains the absolute priority of clinical and research teams, there is a need for research
34
35 426 to continue in a safe way that balances the benefits of continuing programs of research against the
36
37 427 risks from COVID-19. We have amended the study protocol in several ways to reduce any additional
38
39 428 exposure of patients to clinical environments where COVID-19 may be present:

- 40 429 • We have reduced the number of study visits to a minimum. The original study flow diagram is
41
42 430 included in Additional file 1. All interim assessments have been removed in the modified
43
44 431 protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient
45
46 432 clinical care. That is to say, when they attend for their baseline and follow-up study visits they
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48 433 will have their clinical review and clinical blood tests as they would for their normal clinical
49
50 434 care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical
51
52 435 environment over-and-above their normal care.
- 52 436 • The original study design included a 2-week face-to-face training period where participants
53
54 437 would attend the hospital to learn how to complete the exercises and the exercise program
55
56 438 with a member of the research team. This training period will now be done remotely, via video
57
58 439 conferencing, with discussion and feedback over the telephone and using the instructional
59
60 440 videos and literature that support the home-based exercise intervention.

- 1
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3 441 • When participants attend for their study visits, departmental procedures have been updated
4
5 442 to now include meticulous cleaning of all equipment before and after use, one-way flows of
6
7 443 participants to ensure participants do not mix, and the use of personal protective equipment
8
9 444 for all staff and participants.

10 445 The above changes have been agreed with the local REC and the study sponsor and have allowed
11
12 446 recommencement of study recruitment and procedures.

14 447 **DISCUSSION**

16 448 This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise
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18 449 intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on
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20 450 cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare
21
22 451 utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial
23
24 452 to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR
25
26 453 to evaluate the structural and functional changes of the heart in this at risk population.

27 454 Qualitative data will provide valuable personal perspectives on the acceptability of this specific
28
29 455 exercise program. Transplant recipients experience complex medical journeys and are likely to have
30
31 456 specific unmet needs in the area of exercise and lifestyle. This will be valuable information for future
32
33 457 randomised controlled trials (RCTs) and exercise guideline development.

34 458 Home-based intervention outcomes are reliant on accurate reporting by participants with regards to
35
36 459 frequency, intensity, and duration of exercise performed. This is often a limitation of unsupervised
37
38 460 interventions. We will ensure participants are correctly advised of how to monitor and report their
39
40 461 exercise completion throughout the trial and encourage this through telephone communications.

41 462 We anticipate that a positive outcome will lead to both an increased understanding of the specific
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43 463 exercise requirements of KTRs and the development of new programs that promote longer-term
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45 464 engendered lifestyle change that can be incorporated into standard practice with much lower financial
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47 465 implications than in-centre supervised rehabilitation.

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3 473 **DECLARATIONS**
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6 475 **Ethical issues**
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10 477 University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the
11 478 East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref
12 479 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on
13 480 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio
14 481 on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was
15 482 prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). This manuscript is
16 483 quorate with the most recent approved protocol (version 5 01.05.2020). Relevant parties will be
17 484 informed of any substantial protocol modifications. Steps have been taken when designing this
18 485 protocol to minimise the ethical implications and ensure patient welfare. The study will comply with
19 486 the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the
20 487 Research Governance Framework for Health and Social Care.
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30 489 **Twitter:** REB, @RBillany; MGB, @DrMattGB.
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32 490

33 491 **Author contributions:** MGB is the chief investigator for this trial. REB and MGB wrote this manuscript.
34 492 All authors contributed to the development of the study design and protocol lead by MGB. All authors
35 493 reviewed and approved the final version of this manuscript.
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39 494

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42 497 management, analysis, and interpretation of data; writing of the report; or the decision to submit the
43 498 report for publication.
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46

47 499

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50 502 necessarily those of the NHS, the NIHR or the Department of Health.
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55 504 **Competing interests:** None declared.
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3 506 **Availability of data:** On completion the results of this study will be published in peer-reviewed journals
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5 507 and presented at national and international conferences. Contributions of all authors to manuscripts
6
7 508 arising from this study will be made explicit in the relevant of each individual journal. Participant level
8
9 509 data will be available following publication of results on request to the Chief Investigator. Results will
10
11 510 also be disseminated to the patient and public community via social media and newsletter articles and
12
13 511 presentations at patient conferences and forums, led by the patient partners. It is anticipated that the
14
15 512 results of this study will inform future design of larger RCTs in this subject area and contribute to
16
17 513 future specific physical activity guidelines in this population.
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19 514

20 515 **Consent for publication:** Not applicable.
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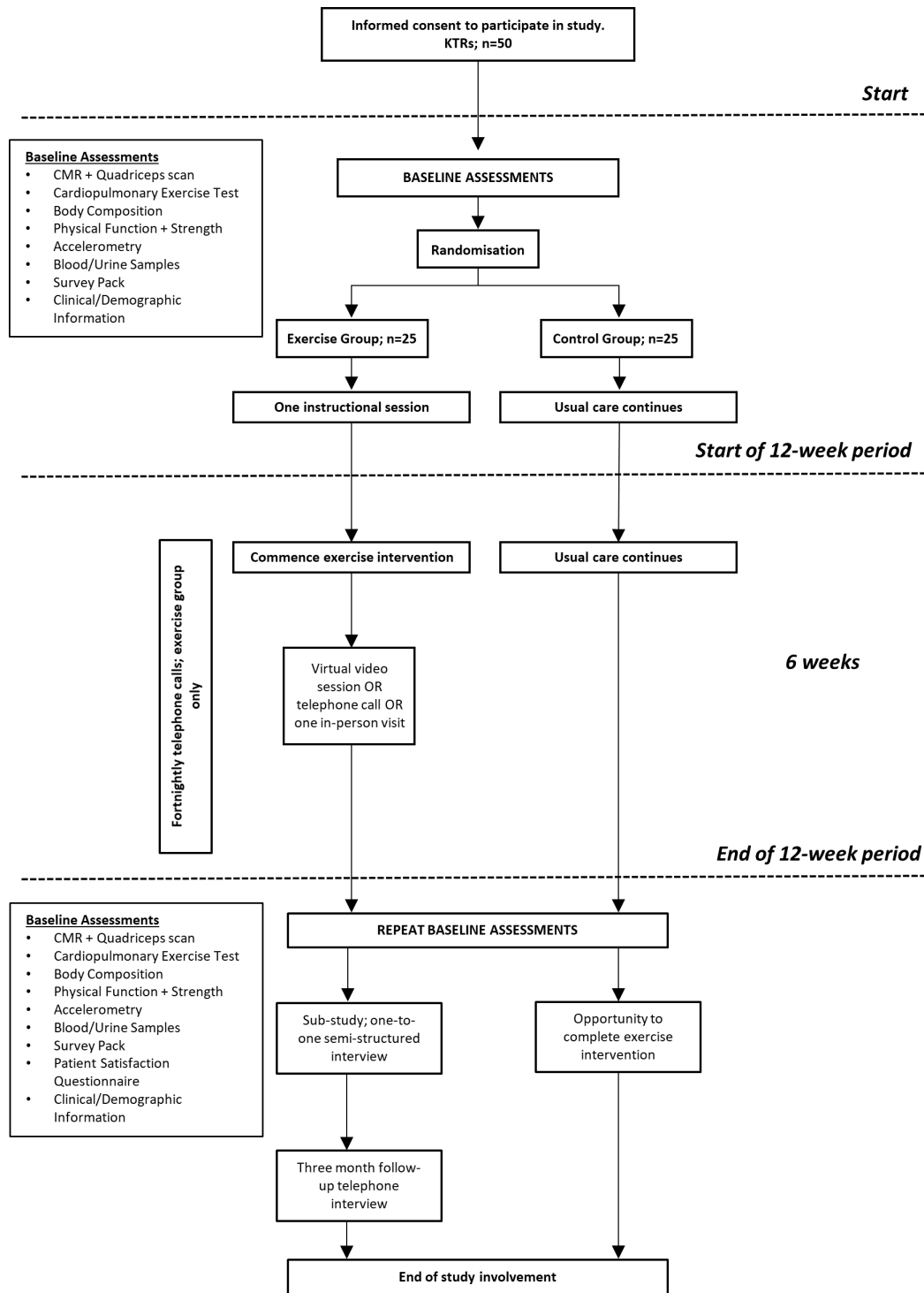
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775 **Tables and Figures**



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779 **Figure 1. ECSERT study flow diagram**

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Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Diabetes mellitus • Dyslipidaemia • Hypertension • Obesity (BMI >30) • History of ischaemic heart disease/cerebrovascular disease 	<ul style="list-style-type: none"> • 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 \geq 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.

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800 **Additional file details**

801 File name: Additional File 1

802 File format: Additional File 1.pdf

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

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

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For peer review only

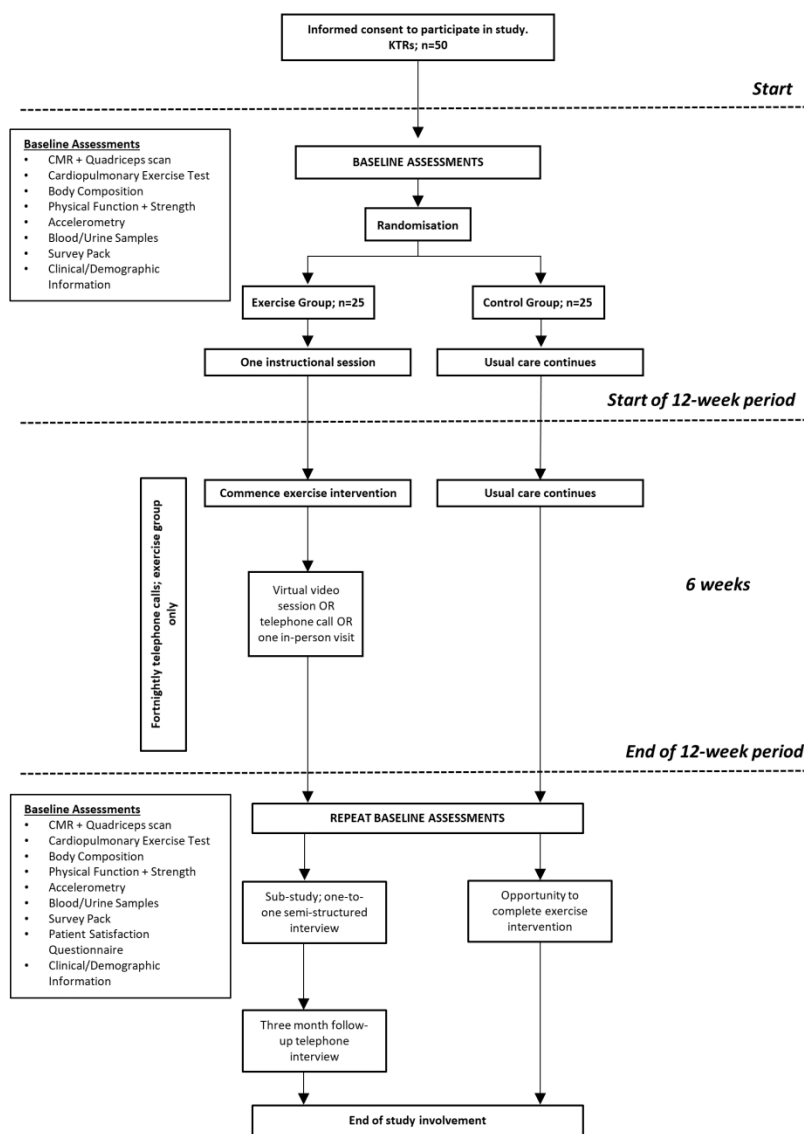


Figure 1. ECSERT study flow diagram

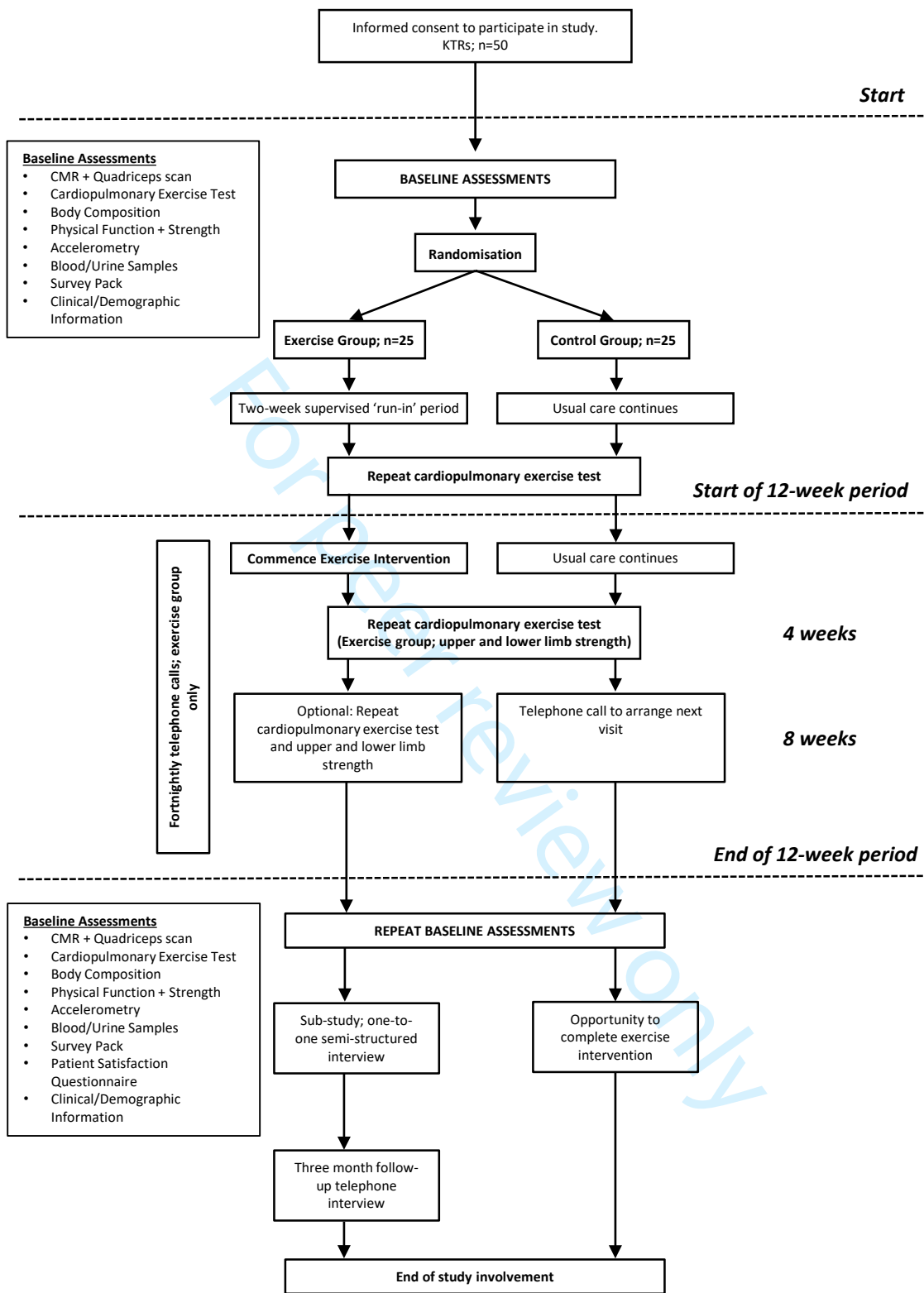


Figure X. Original ECSERT study flow diagram (pre-COVID-19)



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)

1			
2	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)
3			
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8	Methods: Participants, interventions, and outcomes		
9			
10	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)
11			
12			
13			
14	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)
15			
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 5 and 6)
20			
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22		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)
23			
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28		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)
29			
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32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 5, line 164)
33			
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35	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)
36			
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43	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)
44			
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48	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)
49			
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54	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 5, 140+)
55			
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2 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)

10 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)

15 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Page 5, 158)

20 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A

25 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A

29 **Methods: Data collection, management, and analysis**

31 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)

39 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)

44 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)

52 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)

56 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A

1
2 20c Definition of analysis population relating to protocol non-adherence
3 (eg, as randomised analysis), and any statistical methods to handle
4 missing data (eg, multiple imputation) (Page 12)
5

6 **Methods: Monitoring**

7
8 Data monitoring 21a Composition of data monitoring committee (DMC) or Data and Safety
9 Monitoring Board (DCMB); summary of its role and reporting
10 structure; statement of whether it is independent from the sponsor
11 and competing interests; and reference to where further details about
12 its charter can be found, if not in the protocol. Alternatively, an
13 explanation of why a DMC is not needed
14
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17 A DSMB is indicated, from a practical perspective in the following
18 circumstances:

- 19
20
21 1. If the trial is intended to provide definitive information about
22 effectiveness and/or safety of a medical or bio-behavioral intervention
23 2. If there are prior data to suggest that the intervention being studied has
24 the potential to induce potentially unacceptable toxicity
25 3. If the trial is evaluating mortality or another major endpoint, such that
26 inferiority of one treatment arm has safety as well as effectiveness
27 implications
28 4. If it would ethically be important for the trial to stop early if the primary
29 question addressed has been definitively answered, even if secondary
30 questions or complete safety information were not yet fully addressed
31

32
33 The ECSERT study does not meet any of these criteria as a pilot/feasibility
34 study

35 21b Description of any interim analyses and stopping guidelines,
36 including who will have access to these interim results and make the
37 final decision to terminate the trial N/A
38

39
40 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
41 spontaneously reported adverse events and other unintended effects
42 of trial interventions or trial conduct (Page 12, safety reporting)
43

44 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
45 whether the process will be independent from investigators and the
46 sponsor N/A aside from usual sponsor audits
47
48

49 **Ethics and dissemination**

50
51 Research ethics 24 Plans for seeking research ethics committee/institutional review
52 approval board (REC/IRB) approval (Page 16, ethical issues)
53

54 Protocol 25 Plans for communicating important protocol modifications (eg,
55 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
56 (eg, investigators, REC/IRBs, trial participants, trial registries,
57 journals, regulators) (Page 16, ethical issues)
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1			
2	Consent or	26a	Who will obtain informed consent or assent from potential trial
3	assent		participants or authorised surrogates, and how (see Item 32) (page 5)
4			
5		26b	Additional consent provisions for collection and use of participant
6			data and biological specimens in ancillary studies, if applicable
7			(consent form)
8			
9	Confidentiality	27	How personal information about potential and enrolled participants
10			will be collected, shared, and maintained in order to protect
11			confidentiality before, during, and after the trial (Page 11)
12			
13	Declaration of	28	Financial and other competing interests for principal investigators for
14	interests		the overall trial and each study site (Page 16, line 515)
15			
16	Access to data	29	Statement of who will have access to the final trial dataset, and
17			disclosure of contractual agreements that limit such access for
18			investigators (Page 17, availability of data)
19			
20			
21	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
22	post-trial care		compensation to those who suffer harm from trial participation N/A
23			
24	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
25	policy		participants, healthcare professionals, the public, and other relevant
26			groups (eg, via publication, reporting in results databases, or other
27			data sharing arrangements), including any publication restrictions
28			(Page 17, availability of data)
29			
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32		31b	Authorship eligibility guidelines and any intended use of professional
33			writers (Page 17, availability of data)
34			
35		31c	Plans, if any, for granting public access to the full protocol,
36			participant-level dataset, and statistical code (Page 17, availability of
37			data)
38			
39			
40	Appendices		
41			
42	Informed consent	32	Model consent form and other related documentation given to
43	materials		participants and authorised surrogates Yes
44			
45	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
46	specimens		specimens for genetic or molecular analysis in the current trial and
47			for future use in ancillary studies, if applicable (Page 10)
48			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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

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Complete List of Authors:	<p>Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences</p> <p>Wilkinson, Thomas ; University of Leicester, Department of Health Sciences</p> <p>Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences</p> <p>Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Brady, Emer; University of Leicester, Department of Cardiovascular Sciences</p> <p>Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Cooper, Nicola; University of Leicester, Department of Health Sciences</p> <p>Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research</p> <p>Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences</p> <p>Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Smith, Alice; University of Leicester, Department of Health Sciences</p> <p>Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p>

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





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3 1 **A pilot randomised controlled trial of a structured, home-based exercise program on**
4
5 2 **cardiovascular structure and function in kidney transplant recipients: The ECSERT study**
6
7 3 **design and methods**
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9 4

10 5 Roseanne E Billany^{1,2}, Noemi Vadaszy³, Nicolette C Bishop⁴, Thomas J Wilkinson³, Sherna Adenwalla^{1,2},
11 6 Katherine A Robinson¹, Kathryn Croker², Emer M Brady¹, Joanne Wormleighton⁵, Kelly Parke^{1,5}, Nicola
12 7 J Cooper³, Angela C Webster⁶, Jonathan Barratt^{1,2}, Gerry P McCann¹, James O Burton^{1,2,5}, Alice C Smith³,
13 8 Matthew PM Graham-Brown^{1,2}
14
15
16
17 9

18
19 10 ¹ Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

20 11 ² John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

21 12 ³ Department of Health Sciences, University of Leicester, Leicester, UK

22 13 ⁴ School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

23 14 ⁵ Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK

24 15 ⁶ Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and
25 16 Transplant Research, Westmead Hospital, Sydney, NSW, Australia.
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34 19 **Corresponding author:**

35 20 Dr Matthew Graham-Brown

36 21 Department of Cardiovascular Sciences

37 22 University of Leicester

38 23 Leicester

39 24 United Kingdom

40 25 mgb23@leicester.ac.uk
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27 **Keywords:** kidney transplantation, home-based exercise, cardiovascular disease, feasibility, cardiac
28 MRI

30 **Abstract:** 300

31 **Word count:** 4402

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3 35 **ABSTRACT**
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5 36

6 37 **Background:** Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney
7
8 38 transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by
9
10 39 clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes
11
12 40 in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population,
13
14 41 evidence is limited, and physical activity levels and patient activation towards exercise and self-
15
16 42 management are low. This pilot study will assess the feasibility of delivering a structured, home-based
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18 43 exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the
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20 44 putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality
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22 45 of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise
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24 46 program.
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26 47
27 48 **Methods and analysis:** Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-
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29 49 based combined resistance and aerobic exercise intervention or; (2) the control; usual care.
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31 50 Intervention participants will have one introductory session for instruction and practice of the
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33 51 recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access
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35 52 to instructional videos. The study will evaluate the feasibility of recruitment, randomisation, retention,
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37 53 assessment procedures, and the intervention implementation. Outcomes, to be assessed prior to
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39 54 randomisation and post-intervention, include: cardiac structure and function with stress-perfusion
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41 55 cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of
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43 56 cardiometabolic health, quality of life, and patient activation. These data will be used to inform the
44
45 57 power calculations for future definitive trials.
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48 59 **Ethics and dissemination:** The protocol was reviewed and given favourable opinion by the East
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50 60 Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be
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52 61 published in peer-reviewed academic journals and will be disseminated to the patient and public
53
54 62 community via social media, newsletter articles, and presentations at conferences.
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56 63

57 64 **Trial registration number:** NCT04123951; prospectively registered.
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3 67 **ARTICLE SUMMARY**
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5 68 **Strengths and limitations of this study:**
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- 9 71 • Data on the effects of exercise interventions on the cardiac structural and functional aspects
10 72 of CVD in this population are lacking and baseline values of multiparametric cardiac magnetic
11 73 resonance imaging in KTRs are previously undefined.
 - 12 74 • This study uses a novel home-based exercise intervention with the potential to translate into
13 75 a widespread, low-resource intervention compared to in-centre, supervised interventions
14 76 that are costly and labour intensive.
 - 15 77 • As it can be difficult to ensure control groups are not influenced to change their lifestyle as a
16 78 result of being part of the study; control participants will be offered the intervention after
17 79 completion of the study.
 - 18 80 • This study will provide quantitative and qualitative feasibility and pilot data to inform a
19 81 definitive randomised controlled trial that will explore longer-term engendered lifestyle
20 82 change in this population in response to a complex, home-based, lifestyle intervention.
 - 21 83 • Secondary outcome analysis will identify the putative cardiometabolic and muscular effects
22 84 of the intervention, although these results would need confirming in adequately powered
23 85 studies due to the small sample size of this pilot study.
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86 BACKGROUND

87 Kidney transplantation is the preferred modality of renal replacement therapy for patients with end
88 stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage
89 over remaining on dialysis,¹ cardiovascular disease (CVD) is a leading cause of morbidity, mortality,
90 and graft loss.²⁻⁴ Since 2015, mortality rates attributed to CVD have been rising.⁴ Cardiovascular
91 disease in kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,³
92 ^{5 6} which drive classical atheromatous coronary artery disease, and non-traditional risk factors
93 resulting in pathological changes in cardiovascular structure and function that associate with
94 mortality.⁷ Immunosuppressive agents are well known to drive traditional³ and non-traditional
95 cardiometabolic risk factors.^{8 9} Non-traditional cardiometabolic risk factors, including endothelial
96 dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-mineral
97 metabolism,¹⁰⁻¹² are of at least equal importance in the pathogenesis of CVD in KTRs.⁷ This is further
98 illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate
99 cardiovascular risk in patients with chronic kidney disease (CKD);¹¹⁻¹³⁻¹⁵ coronary revascularisation does
100 not improve outcomes for KTRs as it does in the general population¹² and cardiac events are more
101 likely to be fatal in KTRs.¹⁶

102 Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”,
103 is characterised by stereotypical changes in the cardiovascular structure and function of the heart such
104 as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,¹⁷
105 myocardial fibrosis,¹⁸ and aortic stiffness¹⁹; all of which relate to poor cardiovascular outcomes.^{20 21}
106 Although structural and functional improvements of the heart and vessels have been seen post-
107 transplantation in some studies,²² others have shown no regression²³ and parameters such as LVH are
108 independent factors for cardiac failure and mortality in KTRs.¹⁵ Cardiac magnetic resonance imaging
109 (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown
110 methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic
111 function to be reproducible in patients with kidney disease,²⁴⁻²⁶ making CMR the ideal imaging
112 modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.
113 Numerous epidemiological studies have observed the association between low levels of physical
114 activity and increased prevalence of CVD risk factors,²⁷⁻²⁹ and an inverse relationship between physical
115 activity and all-cause and CVD mortality.^{30 31} Physical activity levels in KTRs are lower than the general
116 population,^{32 33} with only 27% classified as meeting the UK national recommended physical activity
117 levels.³⁴ Whilst physical activity levels improve in the year following transplantation, they plateau after
118 one-year.³³ In the general population, lifestyle changes that increase physical activity through
119 structured exercise lower mortality.^{35 36} Despite this evidence, there is a lack of rigorous research into

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2
3 120 the role of increased physical activity in mitigating cardiovascular risk in KTRs.³⁷ Recent consensus
4 121 recommendations from experts and stakeholders highlighted the need for a priority research agenda
5 122 in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this
6 123 patient population.³⁸ Whilst supervised exercise interventions in KTRs improve cardiorespiratory
7 124 fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic
8 125 profile,³⁹⁻⁴¹ strength,⁴² vascular stiffening,⁴⁰ weight,⁴³ and inflammation,⁴⁴ they are not realistically
9 126 deliverable in the current financial climate and have not translated to clinical practice. Furthermore,
10 127 exercise habits following in-centre supervised programs are not maintained⁴⁵⁻⁴⁷ which can be
11 128 potentially attributed to low levels of patient activation (a measure of a person's skills, confidence,
12 129 and knowledge to manage their own health) and a failure for such programs to engender sustained
13 130 lifestyle changes.^{48 49} Home-based exercise training programs have been shown to be deliverable in
14 131 patients on dialysis and patients undergoing cardiac rehabilitation,⁵⁰⁻⁵³ but the effectiveness and
15 132 deliverability of home-based exercise interventions are largely untested in KTRs. It cannot be assumed
16 133 that such programs will be acceptable to KTRs, whose home-lives, social and occupational
17 134 circumstances are significantly different to dialysis and cardiac patients. Many KTRs have had enforced
18 135 sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as
19 136 well as the disease processes at work may be different.^{54 55}

137 **Objectives**

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

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

148 Two sub-studies will assess:

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

152

153 **METHODS AND ANALYSIS**

154 **ECSERT trial design**

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

157 **Participant identification and recruitment**

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

169 **Randomisation**

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

176 **Intervention and comparator arms**

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

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

181 *Aerobic component*

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

1
2
3 185 be collected throughout cardiopulmonary exercise tests (CPET) and participants will be educated on
4
5 186 its use during the instructional session(s). RPE will be utilised rather than heart rate for two reasons:
6
7 187 (1) Many patients are on medication which impacts heart rate (e.g. beta-blockers). We therefore
8
9 188 cannot ascertain a true maximal heart rate from the exercise test in order for them to safely (and
10
11 189 reliably) monitor intensity this way without supervision. (2) This is a pragmatic decision based on the
12
13 190 potential for translation into low-cost future studies and clinical practice. However, should
14
15 191 participants in the trial already own a smart watch or heart rate monitor, we would not discourage
16
17 192 them from using it if they desire.

17 193 *Resistance component*

19 194 The resistance component of the exercise intervention will include a combination of 6-8 exercises per
20
21 195 session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper
22
23 196 and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool
24
25 197 of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row,
26
27 198 reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has
28
29 199 modifications for different abilities and may be pragmatically adjusted or changed throughout the
30
31 200 study as required. These exercises were chosen based on their ability to be modified, their subjective
32
33 201 difficulty, and their safety when being performed by participants new to exercise in an unsupervised
34
35 202 environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on
36
37 203 consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of
38
39 204 10 repetitions (at approximately 60% of estimated 1 repetition maximum (RM)⁵⁷), gradually increasing
40
41 205 to 3-6 sets of 10 repetitions over the study period with a minimum of 30 sec rest between sets. These
42
43 206 figures may be adjusted to accommodate different abilities and different rates of progression. Where
44
45 207 equipment is limited (e.g. participants reach the highest provided dumbbell weight), participants will
46
47 208 be advised to increase the number of sets performed. The load chosen was based on previous research
48
49 209 which suggests whilst heavier loads (>60% of 1RM) are favoured for increasing strength, the effect
50
51 210 size is still large for lighter loads (<60% of 1RM) and both are effective for increasing muscle size.⁵⁸ It
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53 211 is important not to discourage inactive or inexperienced participants with very heavy loads.
54
55 212 Participants will be provided with an exercise diary which includes additional instructions, dumbbells
56
57 213 and resistance bands, and access to educational and instructional videos. Instructional videos will
58
59 214 include: the importance of an active and healthy lifestyle, the importance of warming up and cooling
60
215 down and how to do it, a reminder of how to use the RPE scale, demonstrations of each resistance
216
217 exercise, and information about the aerobic component (videos can be viewed here:
218 https://www.youtube.com/playlist?list=PLwbE3AF9Ej_VuI5uoiF-C9Cl8wrgKz5Nv). Participants will
receive a telephone call from a member of the research team every two weeks in order to discuss

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

222 Control group: 'Usual care'

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

232 Study timeline

233 Baseline assessments

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

237 *Collection of routine clinical information and cost-effectiveness*

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

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

247 *Cardiac stress MRI*

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

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3 251 contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m² will be given for
4
5 252 perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m² will undergo
6
7 253 non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

- 8
9 254 • Left and right-ventricular structure and function (left ventricular mass, left and right
10
11 255 ventricular volumes and ejection fractions);⁵⁹
12
13 256 • Tissue-characterisation with native and post-contrast T1 mapping and delayed gadolinium
14
15 257 enhancement;⁶⁰⁻⁶²
16
17 258 • Myocardial systolic-strain and peak early-diastolic strain rate;²⁶
18
19 259 • Quantitative perfusion imaging (coronary blood-flow to quantify coronary reserve and
20
21 260 ischaemia);⁶³
22
23 261 • Aortic distensibility.²⁴

24 262 *Quadriceps MRI*

25 263 At the end of the CMR scan, participants will immediately undergo an MRI scan of the quadriceps
26
27 264 muscle in their right leg to assess muscle size (volume) as previously described⁶⁴

28 265 *Cardiopulmonary exercise test*

29
30 266 A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked
31
32 267 cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W)
33
34 268 every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min⁶⁵. Participants will be
35
36 269 encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured
37
38 270 (VO_{2peak}) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true
39
40 271 maximal (plateau) VO₂ (VO_{2max}) is less commonly achieved in deconditioned and/or clinical patients.
41
42 272 Test data will be considered usable if respiratory exchange ratio is ≥1.00 and RPE is ≥18. The test will
43
44 273 be in the presence of a cardiac nurse to confirm safety to commence exercise training. Blood pressure
45
46 274 will be assessed at baseline and every two minutes throughout the test. A continuous 12-lead
47
48 275 electrocardiogram (ECG) will be monitored throughout. A non-invasive monitor (Moxy, Fortiori Design
49
50 276 LLC., Minnesota, USA) will be worn on the quadriceps muscle which uses near infrared spectroscopy
51
52 277 (NIRS) to measure local oxygen saturation (SmO₂) and total haemoglobin (THb) of the muscle.

53 278 *Lower limb Strength and muscular endurance*

54 279 Isometric and isokinetic muscle (knee extension) strength, of the dominant leg, will be assessed using
55
56 280 a dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA). Peak isometric
57
58 281 strength (torque, Nm) will be assessed from three repetitions of maximum effort at 90° knee flexion
59
60 282 for ~3-5 sec with 60 sec rest. Isokinetic strength will be assessed at three speeds for one set of five

1
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3 283 repetitions at each speed: 60°/sec, 90°/sec, and 120°/sec. Participants will perform a 'sit-to-stand-60'
4
5 284 (STS-60) test measuring how many sit-to-stand cycles can be performed over 60 sec.

6
7 285 *Handgrip strength*

8
9 286 Peak grip strength of the left and right hands will be assessed with a hand dynamometer (Jamar Plus+;
10
11 287 Sammons Preston, Bolingbrook, IL). Each hand will be alternatively tested for three attempts each and
12
13 288 the highest value on each hand will be recorded.

14
15 289 *Gait speed*

16
17 290 A 4 m walk test will be used to assess gait speed. Participants will be asked to walk 4 m at their 'usual
18
19 291 walking pace' for one practice and two, timed trials. The average score (m/sec) of the timed trials will
20
21 292 be recorded.

22
23 293 *Functional mobility*

24
25 294 The 'timed-up-and-go' test (TUAG) will be used to assess functional mobility.^{66 67} The participant is
26
27 295 timed whilst rising from the seated position on a chair, walking 3 m, turning around, and returning to
28
29 296 a seated position.

30
31 297 *Balance and postural stability*

32
33 298 Postural stability and balance will be assessed using a previously reported method⁶⁸ with a FysioMeter
34
35 299 device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to
36
37 300 software on a portable computer (FysioMeter ApS, Brønderslev, Denmark). Total centre of pressure
38
39 301 ellipse area (mm²) will be obtained.

40
41 302 *Quadriceps ultrasound and myotonometry*

42
43 303 Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D
44
45 304 ultrasonography (Hitachi EUB-6500; probe frequency, 7.5 MHz) under resting conditions with the
46
47 305 participant lying prone at a 45° as previously described.⁶⁴ Rectus femoris and vastus lateralis thickness,
48
49 306 subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of the
50
51 307 viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be
52
53 308 obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

54
55 309 *Anthropometric measures*

56
57 310 Anthropometric measures of height, body mass, and waist and hip circumference will be attained in
58
59 311 accordance with standard protocols.⁶⁹ Bioelectrical impedance analysis (BIA) performed on an InBody
60
312 analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat
313
percentage, fat-free mass).^{70 71}

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3 314 *Survey pack*
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5 315 Participants will be provided with a survey pack containing the following questionnaires:
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- 7 316 (1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the
8 presence and severity of disease related symptoms. The I-POS-Renal was developed based on
9 317 the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms
10 318 common in CKD such as pruritus and restless legs.⁷²
11 319
12 320 (2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess
13 generic health outcomes from the patient's perspective.⁷³
14 321
15 322 (3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item
16 multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert
17 323 scale that covers physical fatigue, functional fatigue, emotional fatigue, and social
18 324 consequences of fatigue with excellent internal consistency and test-retest reliability.^{74 75}
19 325
20 326 (4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality
21 and disturbances over a 1-month time interval.⁷⁶
22 327
23 328 (5) Patient Activation Measure (PAM): a validated, licenced tool measuring the spectrum of
24 knowledge, skills, and confidence in patients and capturing the extent to which they feel
25 329 engaged and confident in taking care of their condition ('activation').⁷⁷
26 330
27 331 (6) Brief Health Literacy Screen (BHLS): a 3-item questionnaire to identify inadequate health
28 literacy,⁷⁸ validated against longer screening tools in populations with ESKD.^{79 80}
29 332
30 333 (7) The Global Physical Activity Questionnaire (GPAQ): developed by the World Health
31 Organisation (WHO) for physical activity surveillance in countries. It collects information on
32 334 physical activity participation in three settings or domains (activity at work, travel to and from
33 335 places, and recreational activities) as well as sedentary behaviour, comprising 16 questions.⁸¹
34 336
35 337 (8) Duke Activity Status Index (DASI): a 12-item questionnaire that uses self-reported physical
36 work capacity to estimate peak metabolic equivalents and has been shown to be a valid
37 338 measurement of functional capacity.⁸²
38 339

39 340 *Habitual physical activity*
40

41 341 Objective data on habitual physical activity levels over a 7-day period (ideal minimum 6-days)⁸³ will be
42 342 gained from tri-axial accelerometers (GENEActiv, ActivInsights Ltd., Cambridge, UK). Participants will
43 343 receive the monitor at the baseline and follow-up assessments and will be asked to wear it from
44 344 midnight that evening for 7 days.
45

46 345 *Blood and urine sampling*
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346 Venous blood (30 ml) will be collected using venepuncture of the antecubital vein and prepared and
347 stored appropriately for the following analysis:

- 348 • Circulating markers of cardiovascular disease
- 349 • Circulating markers of systemic inflammation and oxidative stress
- 350 • Blood glucose and HbA1c
- 351 • Lipids and triglycerides
- 352 • Full blood count and renal profile

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

354 Follow-up assessments

355 Follow up visits are summarised in Figure 1. An instructional session (or more if required) following
356 baseline assessments will allow the intervention group to become familiar with the exercise
357 requirements and allow the research team to ensure safety and competence before commencing the
358 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-
359 week period for the intervention group only, participants will be invited to review exercise progression
360 (via video call or in-person), particularly if participants are struggling to undertake the requisite
361 amount of exercise, and as a refresher of the intervention. This combined with regular contact from
362 research staff should aid participant compliance and monitoring.

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

370 **Sub-studies**

371 Additional informed consent will be sought for:

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

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2
3 378 intervention, and study design. Participants who withdraw before the end of the intervention
4
5 379 will also be invited to attend, although in line with ethical standards, this will be optional.
6

7 380 **Sample size**

8
9 381 The purpose of this pilot study is to obtain appropriate data to adequately power future definitive
10
11 382 trials;⁸⁴ a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on
12
13 383 accepted values to provide adequate estimates of standard deviations for future power calculations.⁸⁵
14

15 384 **Data collection and management**

16
17 385 Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will
18
19 386 be entered into a secure database and will only be accessible on password-protected computers at
20
21 387 UHL and University of Leicester by relevant members of the study team. No identifying information
22
23 388 will be kept in electronic form. All source data and original participant identities will be kept in a locked
24
25 389 office in the trial site file only at UHL.

26 390 **Data analysis**

27
28 391 Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous
29
30 392 data to be expressed as mean (\pm standard deviation), if normally distributed or median (interquartile
31
32 393 range) if not. To investigate the differences between interventions we will use analysis of (co-)
33
34 394 variance. Independent samples t-tests and Mann-Whitney U tests will be used assess for baseline
35
36 395 differences between variables for normally and non-normally distributed data respectively. These
37
38 396 data will be used to inform the power calculation for future definitive trials.

39 397 Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive
40
41 398 thematic analysis to explore themes emerging from patient journeys through, and experiences of, the
42
43 399 interventions and outcome measures.

44 400 Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

- 45
46 401 • *Eligibility*: the percentage of patients screened who are eligible.
- 47
48 402 • *Recruitment rate*: the percentage of patients eligible who consent to the trial and the monthly
49
50 403 recruitment rate.
- 51
52 404 • *Adherence to the exercise intervention*: the number of completed sessions per week and
53
54 405 specific intensity and durations achieved.
- 55
56 406 • *Acceptability of randomisation*: comparison of the final group characteristics and
57
58 407 identification of any stratification variables, if applicable.
- 59
60 408 • *Attrition rate*: the number of participants that drop-out of the study.
- 409 • *Outcome acceptability*: the percentage of missing data for each outcome measure.

- 1
2
3 410 • *Safety*: The number of self-reported injuries or adverse events throughout the trial.
4

5 411 The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility ($\geq 50\%$),
6 412 recruitment success of 20% of eligible participants (≥ 2 participants per month), adherence (an average
7 413 of 3 exercise sessions per week) and attrition ($\leq 30\%$).
8
9

10 414 **Safety reporting**

11
12
13 415 All adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) or serious
14 416 adverse reactions (SARs) will be recorded from the time a patient enters the study to the final study
15 417 visit. Each AE or AR will be considered for severity, causality, and expectedness and may be reclassified
16 418 as an SAE or SAR if required.
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20 419 An SAE is any AE that:

- 21 420 • is life threatening
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23 421 • requires hospitalization or prolongation of a hospital admission
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25 422 • results in a persistent or significant disability/incapacity
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27 423 • is a congenital anomaly
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29 424 • results in death

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31 425 All AEs and ARs will be documented in participants CRFs, medical notes, and an AE log and will record
32 426 the following information: description, date of onset and end date, severity, assessment of
33 427 relatedness to study, other suspect device and action taken. Only AEs that are judged to be related to
34 428 the study intervention or procedures will be reported to the sponsor.

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37 429 All SAEs will be reported by the investigators to the sponsor within 24 hours of discovery or notification
38 430 and the report will be signed by the chief investigator within 7 days. If the SAE is deemed related to
39 431 the research procedures or intervention and is unexpected, a report will be sent to the research ethics
40 432 committee (REC) within 15 days.
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42 433 **Patient and public involvement**

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46 434 A patient and public involvement (PPI) group has been convened and will meet with the research team
47 435 to review progress and address issues that arise throughout the duration of the study. The PPI partners
48 436 will assist in the interpretation and dissemination of results. The trial was designed in consultation
49 437 with PPI partners who advised on intervention content and outcome measure acceptability, paying
50 438 particular attention to patient burden, ensuring outcome measures would not over-burden
51 439 participants. The PPI group approved the final design and duration of this intervention and advised
52 440 the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise
53 441 capability.
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60 442 **Changes to the study protocol following the COVID-19 pandemic**

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3 443 The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst
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5 444 patient safety remains the absolute priority of clinical and research teams, there is a need for research
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7 445 to continue in a safe way that balances the benefits of continuing programs of research against the
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9 446 risks from COVID-19. We have amended the study protocol in several ways to reduce any additional
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11 447 exposure of patients to clinical environments where COVID-19 may be present:

- 12 448 • We have reduced the number of study visits to a minimum. The original study flow diagram is
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14 449 included in Additional file 1. All interim assessments have been removed in the modified
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16 450 protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient
17
18 451 clinical care. That is to say, when they attend for their baseline and follow-up study visits they
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20 452 will have their clinical review and clinical blood tests as they would for their normal clinical
21
22 453 care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical
23
24 454 environment over-and-above their normal care.
- 25 455 • The original study design included a 2-week face-to-face training period where participants
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27 456 would attend the hospital to learn how to complete the exercises and the exercise program
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29 457 with a member of the research team. This training period will now be done remotely, via video
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31 458 conferencing, with discussion and feedback over the telephone and using the instructional
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33 459 videos and literature that support the home-based exercise intervention.
- 34 460 • When participants attend for their study visits, departmental procedures have been updated
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36 461 to now include meticulous cleaning of all equipment before and after use, one-way flows of
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38 462 participants to ensure participants do not mix, and the use of personal protective equipment
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40 463 for all staff and participants.

41 464 The above changes have been agreed with the local REC and the study sponsor and have allowed
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43 465 recommencement of study recruitment and procedures.

44 466 **DISCUSSION**

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46 467 This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise
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48 468 intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on
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50 469 cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare
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52 470 utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial
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54 471 to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR
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56 472 to evaluate the structural and functional changes of the heart in this at risk population.

57 473 Qualitative data will provide valuable personal perspectives on the acceptability of this specific
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59 474 exercise program. Transplant recipients experience complex medical journeys and are likely to have
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3 475 specific unmet needs in the area of exercise and lifestyle. This will be valuable information for future
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5 476 randomised controlled trials (RCTs) and exercise guideline development.
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7 477 Home-based intervention outcomes are reliant on accurate reporting by participants with regards to
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9 478 frequency, intensity, and duration of exercise performed. This under-reporting is often a limitation of
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11 479 unsupervised interventions. We will ensure participants are correctly advised of how to monitor and
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13 480 report their exercise completion throughout the trial and encourage this through telephone
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15 481 communications.

16 482 We anticipate that a positive outcome will lead to both an increased understanding of the specific
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18 483 exercise requirements of KTRs and the development of new programs that promote longer-term
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20 484 engendered lifestyle change that can be incorporated into standard practice with much lower financial
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22 485 implications than in-centre supervised rehabilitation.
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3 489 **DECLARATIONS**

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6 491 **Ethical issues**

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10 493 University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the
11 494 East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref
12 495 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on
13 496 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio
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15 497 on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was
16 498 prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). The first participant was
17 499 recruited on 09/03/2020. The predicted study end date is 31/12/2022. This manuscript is quorate with
20 500 the most recent approved protocol (version 6 26.08.2020). Relevant parties will be informed of any
21
22 501 substantial protocol modifications. Steps have been taken when designing this protocol to minimise
23 502 the ethical implications and ensure patient welfare. The study will comply with the International
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25 503 Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research
26 504 Governance Framework for Health and Social Care.
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31 506 **Dissemination:** On completion the results of this study will be published in peer-reviewed journals
32 507 and presented at national and international conferences. Contributions of all authors to manuscripts
33 508 arising from this study will be made explicit in the relevant of each individual journal. Participant level
34 509 data will be available following publication of results on request to the Chief Investigator. Results will
35 510 also be disseminated to the patient and public community via social media and newsletter articles and
36 511 presentations at patient conferences and forums, led by the patient partners. It is anticipated that the
37 512 results of this study will inform future design of larger RCTs in this subject area and contribute to
38 513 future specific physical activity guidelines in this population.
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46 515 **Twitter:** REB, @RBillany; MGB, @DrMattGB.

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50 517 **Author contributions:** MGB is the chief investigator for this trial. REB and MGB are responsible for the
51 518 study design, study setup, completion of study visits, drafting the manuscript, revision of the
52 519 manuscript, and finalising the manuscript. NCB, TJW, KAR, KC, EMB, NJC, ACW, JB, GPM, JOB, and ACS
53 520 are responsible for the study design, drafting the manuscript, and revision of the manuscript. NV, SA,
54 521 JW, and KP are responsible for completion of study visits, drafting the manuscript, and revision of
55 522 manuscript.
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Consent for publication: Not applicable.

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3 786 **Tables and Figures**

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7 788 **See uploaded.**

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9 789 **Figure 1. ECSERT study flow diagram**

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Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
RTRs	
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Diabetes mellitus • Dyslipidaemia • Hypertension • Obesity (BMI >30) • History of ischaemic heart disease/cerebrovascular disease 	<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • Age <18 years • No documented history of major cardiorespiratory chronic condition • None of the following cardiometabolic risk factors: <ul style="list-style-type: none"> • Diabetes mellitus • Dyslipidaemia • Hypertension • History of ischaemic heart disease/cerebrovascular disease • Obesity (BMI>30) • Not on any medication 	<ul style="list-style-type: none"> • 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 \geq 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.

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3 799 **Additional file details**
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5 800 File name: Additional File 1

6 801 File format: Additional File 1.pdf
7

8 802 Title of data: Original ECSERT flow diagram (pre-COVID-19)
9

10 803 Description of data: Flow diagram prior to COVID-19 amendments
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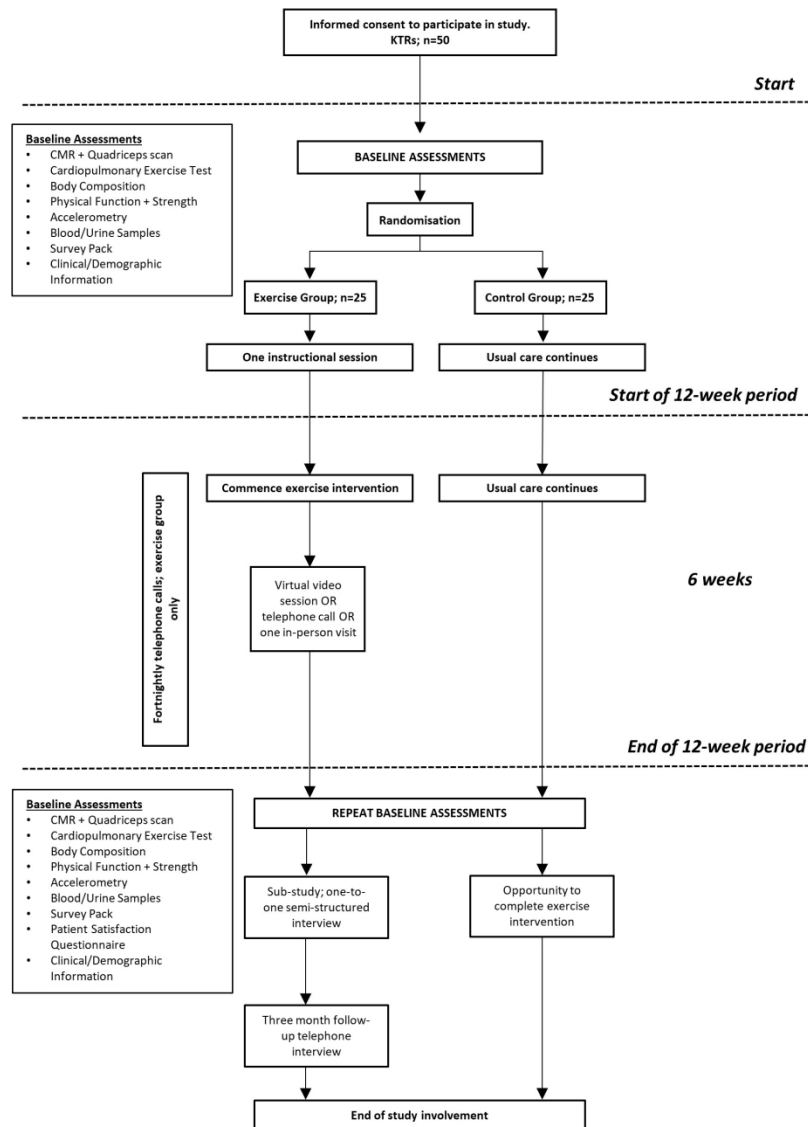


Figure 1 ECSERT Study Flow Diagram

170x219mm (300 x 300 DPI)

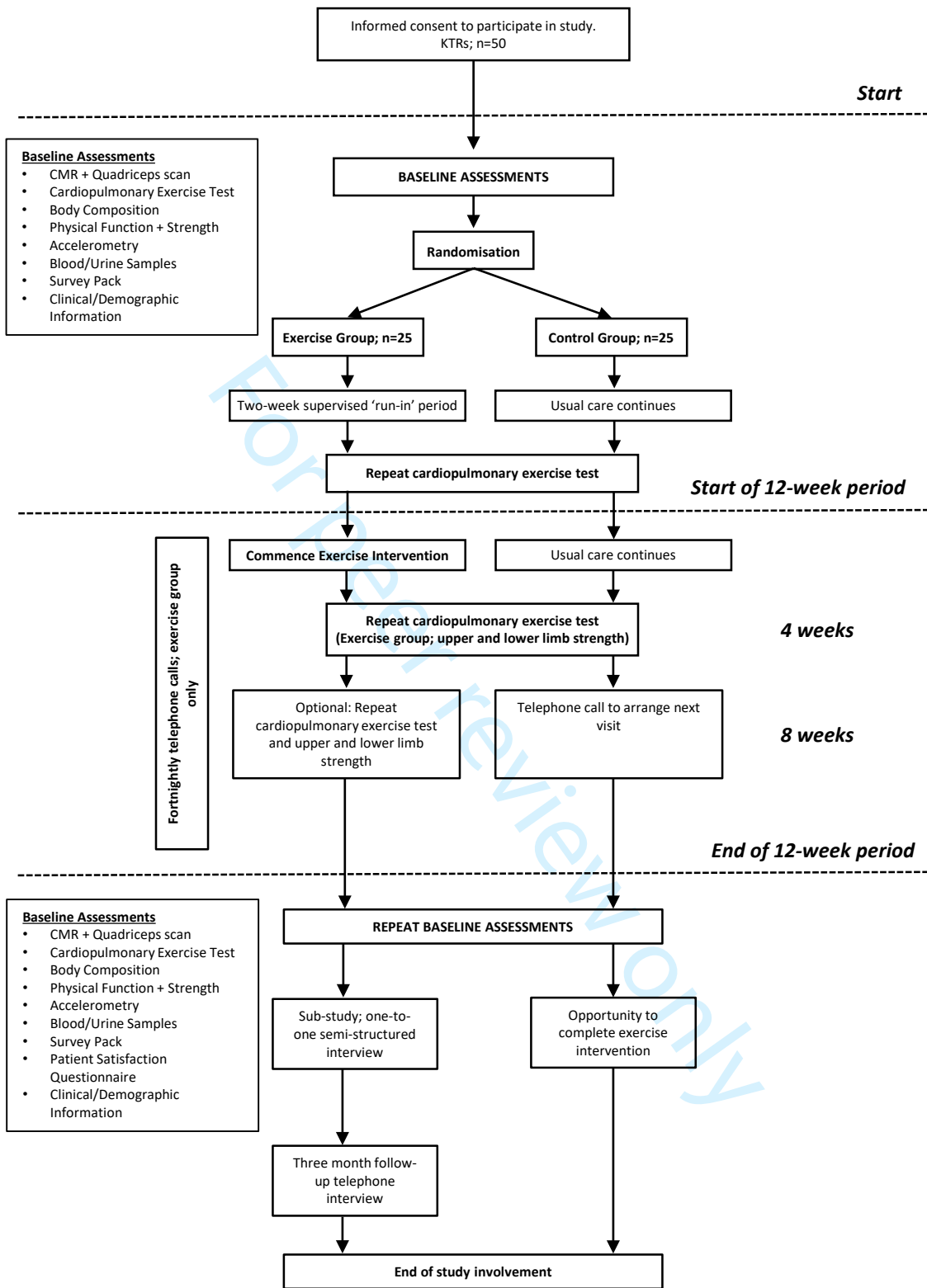


Figure X. Original ECSERT study flow diagram (pre-COVID-19)



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)

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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:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any
5			planned restriction (eg, blocking) should be provided in a separate
6			document that is unavailable to those who enrol participants or
7			assign interventions (Page 5, 154-159)
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Page 5, 154-159)
14			
15	Implementatio	16c	Who will generate the allocation sequence, who will enrol
16	n		participants, and who will assign participants to interventions (Page
17			5, 158)
18			
19			
20	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
21	(masking)		participants, care providers, outcome assessors, data analysts), and
22			how N/A
23			
24		17b	If blinded, circumstances under which unblinding is permissible, and
25			procedure for revealing a participant's allocated intervention during
26			the trial N/A
27			
28			
29	Methods: Data collection, management, and analysis		
30			
31	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
32	methods		trial data, including any related processes to promote data quality
33			(eg, duplicate measurements, training of assessors) and a
34			description of study instruments (eg, questionnaires, laboratory tests)
35			along with their reliability and validity, if known. Reference to where
36			data collection forms can be found, if not in the protocol (Page 7-11)
37			
38			
39		18b	Plans to promote participant retention and complete follow-up,
40			including list of any outcome data to be collected for participants who
41			discontinue or deviate from intervention protocols (Page 11)
42			
43	Data	19	Plans for data entry, coding, security, and storage, including any
44	management		related processes to promote data quality (eg, double data entry;
45			range checks for data values). Reference to where details of data
46			management procedures can be found, if not in the protocol (Page
47			11, lines 349-
48			354)
49			
50			
51	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
52	methods		Reference to where other details of the statistical analysis plan can
53			be found, if not in the protocol (Page 11 and 12)
54			
55		20b	Methods for any additional analyses (eg, subgroup and adjusted
56			analyses) N/A
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2 20c Definition of analysis population relating to protocol non-adherence
3 (eg, as randomised analysis), and any statistical methods to handle
4 missing data (eg, multiple imputation) (Page 12)
5

6 **Methods: Monitoring**

7
8 Data monitoring 21a Composition of data monitoring committee (DMC) or Data and Safety
9 Monitoring Board (DCMB); summary of its role and reporting
10 structure; statement of whether it is independent from the sponsor
11 and competing interests; and reference to where further details about
12 its charter can be found, if not in the protocol. Alternatively, an
13 explanation of why a DMC is not needed
14
15

16
17 A DSMB is indicated, from a practical perspective in the following
18 circumstances:

- 19
20
21 1. If the trial is intended to provide definitive information about
22 effectiveness and/or safety of a medical or bio-behavioral intervention
23 2. If there are prior data to suggest that the intervention being studied has
24 the potential to induce potentially unacceptable toxicity
25 3. If the trial is evaluating mortality or another major endpoint, such that
26 inferiority of one treatment arm has safety as well as effectiveness
27 implications
28 4. If it would ethically be important for the trial to stop early if the primary
29 question addressed has been definitively answered, even if secondary
30 questions or complete safety information were not yet fully addressed
31

32
33 The ECSERT study does not meet any of these criteria as a pilot/feasibility
34 study

35 21b Description of any interim analyses and stopping guidelines,
36 including who will have access to these interim results and make the
37 final decision to terminate the trial N/A
38

39
40 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
41 spontaneously reported adverse events and other unintended effects
42 of trial interventions or trial conduct (Page 12, safety reporting)
43

44 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
45 whether the process will be independent from investigators and the
46 sponsor N/A aside from usual sponsor audits
47
48

49 **Ethics and dissemination**

50
51 Research ethics 24 Plans for seeking research ethics committee/institutional review
52 approval board (REC/IRB) approval (Page 16, ethical issues)
53

54 Protocol 25 Plans for communicating important protocol modifications (eg,
55 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
56 (eg, investigators, REC/IRBs, trial participants, trial registries,
57 journals, regulators) (Page 16, ethical issues)
58
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1			
2	Consent or	26a	Who will obtain informed consent or assent from potential trial
3	assent		participants or authorised surrogates, and how (see Item 32) (page 5)
4			
5		26b	Additional consent provisions for collection and use of participant
6			data and biological specimens in ancillary studies, if applicable
7			(consent form)
8			
9	Confidentiality	27	How personal information about potential and enrolled participants
10			will be collected, shared, and maintained in order to protect
11			confidentiality before, during, and after the trial (Page 11)
12			
13	Declaration of	28	Financial and other competing interests for principal investigators for
14	interests		the overall trial and each study site (Page 16, line 515)
15			
16	Access to data	29	Statement of who will have access to the final trial dataset, and
17			disclosure of contractual agreements that limit such access for
18			investigators (Page 17, availability of data)
19			
20			
21	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
22	post-trial care		compensation to those who suffer harm from trial participation N/A
23			
24	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
25	policy		participants, healthcare professionals, the public, and other relevant
26			groups (eg, via publication, reporting in results databases, or other
27			data sharing arrangements), including any publication restrictions
28			(Page 17, availability of data)
29			
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31			
32		31b	Authorship eligibility guidelines and any intended use of professional
33			writers (Page 17, availability of data)
34			
35		31c	Plans, if any, for granting public access to the full protocol,
36			participant-level dataset, and statistical code (Page 17, availability of
37			data)
38			
39			
40	Appendices		
41			
42	Informed consent	32	Model consent form and other related documentation given to
43	materials		participants and authorised surrogates Yes
44			
45	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
46	specimens		specimens for genetic or molecular analysis in the current trial and
47			for future use in ancillary studies, if applicable (Page 10)
48			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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

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Complete List of Authors:	<p>Billany, Roseanne; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Vadaszy, Noemi; University of Leicester, Department of Health Sciences Bishop , Nicolette ; Loughborough University, School of Sport, Exercise and Health Sciences</p> <p>Wilkinson, Thomas ; University of Leicester, Department of Health Sciences</p> <p>Adenwalla, Sherna; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Robinson, Katherine; University of Leicester, Department of Cardiovascular Sciences</p> <p>Croker , Kathryn; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Brady, Emer; University of Leicester, Department of Cardiovascular Sciences</p> <p>Wormleighton, Joanne; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Parke, Kelly; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, Department of Radiology</p> <p>Cooper, Nicola; University of Leicester, Department of Health Sciences</p> <p>Webster, Angela; The University of Sydney, School of Public Health; Westmead Hospital, Centre for Renal and Transplant Research</p> <p>Barratt, Jonathan; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>McCann, Gerry; University of Leicester, Department of Cardiovascular Sciences</p> <p>Burton, James; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p> <p>Smith, Alice; University of Leicester, Department of Health Sciences</p> <p>Graham-Brown, Matthew ; University of Leicester, Department of Cardiovascular Sciences; University Hospitals of Leicester NHS Trust, John Walls Renal Unit</p>

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





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3 1 **A pilot randomised controlled trial of a structured, home-based exercise program on**
4 **cardiovascular structure and function in kidney transplant recipients: The ECSERT study**
5 **design and methods**
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10 Roseanne E Billany^{1,2}, Noemi Vadaszy³, Nicolette C Bishop⁴, Thomas J Wilkinson³, Sherna F
11 Adenwalla^{1,2}, Katherine A Robinson¹, Kathryn Croker², Emer M Brady¹, Joanne Wormleighton⁵, Kelly
12 Parke^{1,5}, Nicola J Cooper³, Angela C Webster⁶, Jonathan Barratt^{1,2}, Gerry P McCann¹, James O
13 Burton^{1,2,5}, Alice C Smith³, Matthew PM Graham-Brown^{1,2}
14
15
16
17

18
19 ¹ Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

20 ² John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

21 ³ Department of Health Sciences, University of Leicester, Leicester, UK

22 ⁴ School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

23 ⁵ Department of Radiology, University Hospitals of Leicester NHS Trust, Leicester, UK

24 ⁶ Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; Centre for Renal and
25 Transplant Research, Westmead Hospital, Sydney, NSW, Australia.
26
27
28
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33
34 **Corresponding author:**

35 Dr Matthew Graham-Brown

36 Department of Cardiovascular Sciences

37 University of Leicester

38 Leicester

39 United Kingdom

40 mgb23@leicester.ac.uk
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47 **Keywords:** kidney transplantation, home-based exercise, cardiovascular disease, feasibility, cardiac
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52 **Abstract:** 300

53 **Word count:** 4402
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2
3 35 **ABSTRACT**
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6 37 **Background:** Cardiovascular disease (CVD) is a major cause of morbidity and mortality in kidney
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8 38 transplant recipients (KTRs). CVD risk scores underestimate risk in this population as CVD is driven by
9
10 39 clustering of traditional and non-traditional risk factors, which lead to prognostic pathological changes
11
12 40 in cardiovascular structure and function. Whilst exercise may mitigate CVD in this population,
13
14 41 evidence is limited, and physical activity levels and patient activation towards exercise and self-
15
16 42 management are low. This pilot study will assess the feasibility of delivering a structured, home-based
17
18 43 exercise intervention in a population of KTRs at increased cardiometabolic risk and evaluate the
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20 44 putative effects on cardiovascular structural and functional changes, cardiorespiratory fitness, quality
21
22 45 of life, patient activation, healthcare utilisation, and engagement with the prescribed exercise
23
24 46 program.
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26 47
27 48 **Methods and analysis:** Fifty KTRs will be randomised 1:1 to: (1) the intervention; a 12-week home-
28
29 49 based combined resistance and aerobic exercise intervention or; (2) the control; usual care.
30
31 50 Intervention participants will have one introductory session for instruction and practice of the
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33 51 recommended exercises prior to receiving an exercise diary, dumbbells, resistance bands, and access
34
35 52 to instructional videos. The study will evaluate the feasibility of recruitment, randomisation, retention,
36
37 53 assessment procedures, and the intervention implementation. Outcomes, to be assessed prior to
38
39 54 randomisation and post-intervention, include: cardiac structure and function with stress-perfusion
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41 55 cardiac magnetic resonance imaging, cardiorespiratory fitness, physical function, blood biomarkers of
42
43 56 cardiometabolic health, quality of life, and patient activation. These data will be used to inform the
44
45 57 power calculations for future definitive trials.
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47 58

48 59 **Ethics and dissemination:** The protocol was reviewed and given favourable opinion by the East
49
50 60 Midlands-Nottingham 2 research ethics committee (ref 19/EM/0209; 14/10/2019). Results will be
51
52 61 published in peer-reviewed academic journals and will be disseminated to the patient and public
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54 62 community via social media, newsletter articles, and presentations at conferences.
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56 63

57 64 **Trial registration number:** NCT04123951; prospectively registered.
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3 67 **ARTICLE SUMMARY**

4
5 68 **Strengths and limitations of this study:**

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8 70
- 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.
- 9 71
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11 73
- 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.
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14 76
- 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.
- 15 77
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17 79
- 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.
- 18 80
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- 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.
- 21 83
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86 BACKGROUND

87 Kidney transplantation is the preferred modality of renal replacement therapy for patients with end
88 stage kidney disease (ESKD). Although kidney transplantation confers a significant survival advantage
89 over remaining on dialysis,¹ cardiovascular disease (CVD) is a leading cause of morbidity, mortality,
90 and graft loss.²⁻⁴ Since 2015, mortality rates attributed to CVD have been rising.⁴ Cardiovascular
91 disease in kidney transplant recipients (KTRs) associates with traditional cardiometabolic risk factors,³
92 ^{5 6} which drive classical atheromatous coronary artery disease, and non-traditional risk factors
93 resulting in pathological changes in cardiovascular structure and function that associate with
94 mortality.⁷ Immunosuppressive agents are well known to drive traditional³ and non-traditional
95 cardiometabolic risk factors.^{8 9} Non-traditional cardiometabolic risk factors, including endothelial
96 dysfunction, systemic inflammation, acute rejection, anaemia, and deranged bone-mineral
97 metabolism,¹⁰⁻¹² are of at least equal importance in the pathogenesis of CVD in KTRs.⁷ This is further
98 illustrated by the fact that traditional CVD risk-stratification tools dramatically underestimate
99 cardiovascular risk in patients with chronic kidney disease (CKD);^{11 13-15} coronary revascularisation does
100 not improve outcomes for KTRs as it does in the general population¹² and cardiac events are more
101 likely to be fatal in KTRs.¹⁶

102 Chronic kidney disease-related cardiomyopathy, which has been termed “Uremic Cardiomyopathy”,
103 is characterised by stereotypical changes in the cardiovascular structure and function of the heart such
104 as left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic dysfunction,¹⁷
105 myocardial fibrosis,¹⁸ and aortic stiffness¹⁹; all of which relate to poor cardiovascular outcomes.^{20 21}
106 Although structural and functional improvements of the heart and vessels have been seen post-
107 transplantation in some studies,²² others have shown no regression²³ and parameters such as LVH are
108 independent factors for cardiac failure and mortality in KTRs.¹⁵ Cardiac magnetic resonance imaging
109 (CMR) is the gold-standard for assessment of ventricular structure and function and we have shown
110 methods for assessment of tissue characterisation, aortopathy, and sub-clinical systolic and diastolic
111 function to be reproducible in patients with kidney disease,²⁴⁻²⁶ making CMR the ideal imaging
112 modality for assessing multiple aspects of prognostically relevant measures of CVD in clinical studies.

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

1
2
3 120 the role of increased physical activity in mitigating cardiovascular risk in KTRs.³⁸ Recent consensus
4 121 recommendations from experts and stakeholders highlighted the need for a priority research agenda
5 122 in exercise for solid organ transplant recipients (SOTRs) to improve cardiovascular outcomes in this
6 123 patient population.³⁹ Whilst supervised exercise interventions in KTRs improve cardiorespiratory
7 124 fitness and a variety of traditional and non-traditional risk factors for CVD, including metabolic
8 125 profile,⁴⁰⁻⁴² strength,⁴³ vascular stiffening,⁴¹ weight,⁴⁴ and inflammation,⁴⁵ they are not realistically
9 126 deliverable in the current financial climate and have not translated to clinical practice. Furthermore,
10 127 exercise habits following in-centre supervised programs are not maintained⁴⁶⁻⁴⁸ which can be
11 128 potentially attributed to low levels of patient activation (a measure of a person's skills, confidence,
12 129 and knowledge to manage their own health) and a failure for such programs to engender sustained
13 130 lifestyle changes.^{49 50} Home-based exercise training programs have been shown to be deliverable in
14 131 patients on dialysis and patients undergoing cardiac rehabilitation,⁵¹⁻⁵⁴ but the effectiveness and
15 132 deliverability of home-based exercise interventions are largely untested in KTRs. It cannot be assumed
16 133 that such programs will be acceptable to KTRs, whose home-lives, social and occupational
17 134 circumstances are significantly different to dialysis and cardiac patients. Many KTRs have had enforced
18 135 sedentary lifestyles prior to transplantation as dialysis patients and their goals for rehabilitation as
19 136 well as the disease processes at work may be different.^{55 56}

137 **Objectives**

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

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

148 Two sub-studies will assess:

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

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45 154 **METHODS AND ANALYSIS**6
7 155 **ECSERT trial design**8
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10 156 This study is a prospective, randomised, open-label, blinded endpoint (PROBE) pilot study. The study
11 157 flowchart is presented in Figure 1.
1213 158 **Participant identification and recruitment**14
15 159 Fifty KTRs with a stable kidney transplant of >1 year will be recruited from University Hospitals of
16 160 Leicester NHS Trust (UHL) kidney transplant outpatient clinic lists. There are approximately 400-420
17 161 KTRs registered in UHL kidney transplant outpatient clinics. Full lists of inclusion and exclusion criteria
18 162 for KTRs are included in Table 1. Patients will be screened by a clinician for eligibility to enter the study.
19 163 Eligible patients will be approached (via telephone, post, or during their routine clinical appointment)
20 164 and will be provided with verbal and written study information and time to consider without further
21 165 contact (at least 24 h). Additionally, eligible patients who have given prior consent to be contacted
22 166 regarding research opportunities will be contacted via post. All patients will be given the opportunity
23 167 to discuss the study in more detail and to consider their participation. Consent will be performed by
24 168 the Chief Investigator (MBG) according to the rules of good clinical practice. Inclusion and exclusion
25 169 criteria for healthy controls is included within Table 1.
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3334 170 **Randomisation**35
36 171 Following baseline assessment, participants will be randomly allocated (1:1) to either; (1) a 12-week
37 172 home-based combined resistance and aerobic exercise intervention (n=25) or; (2) control (n=25;
38 173 receiving usual care). Randomisation will be blocked (using computer-generated random permuted
39 174 blocks with allocation concealment; <https://www.sealedenvelope.com/simple-randomiser/v1/>) to
40 175 ensure periodic balancing. The Clinical Trials Facilitator will perform the randomisation. Given the
41 176 nature of the intervention, it is not possible for the participants to be blinded to their allocation.
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4647 177 **Intervention and comparator arms**48
49 178 Intervention Group: 12-week home-based combined aerobic and resistance training50
51 179 The 12-week, home-based, structured exercise program includes aerobic and resistance training (4-5
52 180 sessions in total per week). Participants will be advised to complete a warm-up and cool-down prior
53 181 to and following each session, respectively. Participants will continue to receive usual clinical care.
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5657 182 *Aerobic component*
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3 183 The aerobic component of the intervention will be walking, jogging, cycling, or similar, depending on
4
5 184 resources available and participant preference. Participants will be asked to complete 2-3 sessions per
6
7 185 week using a rating of perceived of exertion (RPE)⁵⁷ of 13-15 (somewhat hard) for 20-30 min. RPE will
8
9 186 be collected throughout cardiopulmonary exercise tests (CPET) and participants will be educated on
10
11 187 its use during the instructional session(s). RPE will be utilised rather than heart rate for two reasons:
12
13 188 (1) Many patients are on medication which impacts heart rate (e.g. beta-blockers). We therefore
14
15 189 cannot ascertain a true maximal heart rate from the exercise test in order for them to safely (and
16
17 190 reliably) monitor intensity this way without supervision. (2) This is a pragmatic decision based on the
18
19 191 potential for translation into low-cost future studies and clinical practice. However, should
20
21 192 participants in the trial already own a smart watch or heart rate monitor, we would not discourage
22
23 193 them from using it if they desire.

24 194 *Resistance component*

25 195 The resistance component of the exercise intervention will include a combination of 6-8 exercises per
26
27 196 session chosen by the participant from a pool of twelve exercises (to provide variety) targeting upper
28
29 197 and lower body and core muscle groups, using free weights and/or resistance bands. The chosen pool
30
31 198 of exercises include: squat, hip abduction, lunge, calf-raise, side-lunge, bicep-curl, bent-over row,
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33 199 reverse-fly, lateral-raise, chest-press, side-bends, and standing trunk rotation. Each exercise has
34
35 200 modifications for different abilities and may be pragmatically adjusted or changed throughout the
36
37 201 study as required. These exercises were chosen based on their ability to be modified, their subjective
38
39 202 difficulty, and their safety when being performed by participants new to exercise in an unsupervised
40
41 203 environment. Participants will aim to complete 6-8 resistance exercises twice a week (but not on
42
43 204 consecutive days to allow appropriate recovery). Initially they will be advised to complete 1-2 sets of
44
45 205 10 repetitions (at approximately 60% of estimated 1 repetition maximum (RM)⁵⁸), gradually increasing
46
47 206 to 3-6 sets of 10 repetitions over the study period with a minimum of 30 sec rest between sets. The
48
49 207 1RM will be determined after randomisation by an exercise physiologist. These figures may be
50
51 208 adjusted to accommodate different abilities and different rates of progression. Where equipment is
52
53 209 limited (e.g. participants reach the highest provided dumbbell weight), participants will be advised to
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55 210 increase the number of sets performed. The load chosen was based on previous research which
56
57 211 suggests whilst heavier loads (>60% of 1RM) are favoured for increasing strength, the effect size is still
58
59 212 large for lighter loads (<60% of 1RM) and both are effective for increasing muscle size.⁵⁹ It is important
60
213 not to discourage inactive or inexperienced participants with very heavy loads. Participants will be
214
215 provided with an exercise diary which includes additional instructions, dumbbells and resistance
216
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

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

224 Control group: 'Usual care'

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

234 Study timeline

235 **Baseline assessments**

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

239 *Collection of routine clinical information and cost-effectiveness*

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

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

249 *Cardiac stress MRI*

250 All participants will undergo a comprehensive adenosine-stress perfusion CMR scans at baseline and
251 on study-completion. Participants will be scanned on a 3T platform (Skyra, Siemens Medical Imaging,
252 Erlangen, Germany) with an 18-channel phased-array receiver coil. New-generation gadolinium-based
253 contrast agent with a licence for use in patients with an eGFR >30 ml/min/1.73 m² will be given for
254 perfusion and delayed enhancement imaging. Patients with an eGFR <40 ml/min/1.73 m² will undergo
255 non-contrast CMR scanning without gadolinium. Scans will quantitatively define:

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

264 *Quadriceps MRI*

265 At the end of the CMR scan, participants will immediately undergo an MRI scan of the quadriceps
266 muscle in their right leg to assess muscle size (volume) as previously described⁶⁵

267 *Cardiopulmonary exercise test*

268 A CPET utilising a standardised ramp protocol will be performed on a stationary electronically braked
269 cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands) with increasing workload (1 watt (W)
270 every 4 sec (10-15 w/min)) ensuring volitional exhaustion within 12-15 min⁶⁶. Participants will be
271 encouraged to cycle at a continuous cadence (~70 rpm). The highest oxygen uptake will be measured
272 ($\dot{V}O_{2peak}$) using a simultaneous gas analyser (Metalyser 3B CPX System, CORTEX, Germany) as true
273 maximal (plateau) $\dot{V}O_2$ ($\dot{V}O_{2max}$) is less commonly achieved in deconditioned and/or clinical patients.
274 Test data will be considered usable if respiratory exchange ratio is ≥ 1.00 and RPE is ≥ 18 . The test will
275 be in the presence of a cardiac nurse to confirm safety to commence exercise training. Blood pressure
276 will be assessed at baseline and every two minutes throughout the test. A continuous 12-lead
277 electrocardiogram (ECG) will be monitored throughout. A non-invasive monitor (Moxy, Fortiori Design
278 LLC., Minnesota, USA) will be worn on the quadriceps muscle which uses near infrared spectroscopy
279 (NIRS) to measure local oxygen saturation (SmO_2) and total haemoglobin (THb) of the muscle.

280 *Lower limb Strength and muscular endurance*

1
2
3 281 Isometric and isokinetic muscle (knee extension) strength, of the dominant leg, will be assessed using
4
5 282 a dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA).⁶⁷ Peak isometric
6
7 283 strength (torque, Nm) will be assessed from three repetitions of maximum effort at 90° knee flexion
8
9 284 for ~3-5 sec with 60 sec rest. Isokinetic strength will be assessed at three speeds for one set of five
10
11 285 repetitions at each speed: 60°/sec, 90°/sec, and 120°/sec. Participants will perform a 'sit-to-stand-60'
12
13 286 (STS-60) test measuring how many sit-to-stand cycles can be performed over 60 seconds to assess
14
15 287 lower limb muscular endurance.⁶⁸

15 288 *Handgrip strength*

16
17
18 289 Peak grip strength of the left and right hands will be assessed with a hand dynamometer (Jamar Plus+;
19
20 290 Sammons Preston, Bolingbrook, IL). Each hand will be alternatively tested for three attempts each and
21
22 291 the highest value on each hand will be recorded.⁶⁹

23 292 *Gait speed*

24
25 293 A 4 m walk test will be used to assess gait speed. Participants will be asked to walk 4 m at their 'usual
26
27 294 walking pace' for one practice and two, timed trials. The average score (m/sec) of the timed trials will
28
29 295 be recorded.

30 296 *Functional mobility*

31
32
33 297 The 'timed-up-and-go' test (TUAG) will be used to assess functional mobility.^{70 71} The participant is
34
35 298 timed whilst rising from the seated position on a chair, walking 3 m, turning around, and returning to
36
37 299 a seated position.

38 300 *Balance and postural stability*

39
40
41 301 Postural stability and balance will be assessed using a previously reported method⁷² with a FysioMeter
42
43 302 device (modified Nintendo Wii balance-board (Nintendo, Kyoto, Japan)) connected via Bluetooth to
44
45 303 software on a portable computer (FysioMeter ApS, Brønderslev, Denmark). Total centre of pressure
46
47 304 ellipse area (mm²) will be obtained.

48 305 *Quadriceps ultrasound and myotonometry*

49
50 306 Rectus femoris anatomical cross-sectional area will be measured from the right leg using B-mode 2D
51
52 307 ultrasonography (Hitachi EUB-6500; probe frequency, 7.5 MHz) under resting conditions with the
53
54 308 participant lying prone at a 45° as previously described.⁶⁵ Rectus femoris and vastus lateralis thickness,
55
56 309 subcutaneous fat thickness, and fibre pennation angles will be obtained. Measurements of the
57
58 310 viscoelastic properties of the soft tissue above the mid-point of the rectus femoris muscle will be
59
60 311 obtained using a myotonometry device (MyotonPro, Tallinn, Estonia).

1
2
3 312 *Anthropometric measures*
4

5 313 Anthropometric measures of height, body mass, and waist and hip circumference will be attained in
6
7 314 accordance with standard protocols.⁷³ Bioelectrical impedance analysis (BIA) performed on an InBody
8
9 315 analyser (InBody 370, Chicago, Illinois, USA) will be used to estimate body composition (eg. body fat
10
11 316 percentage, fat-free mass).^{74 75}

12
13 317 *Survey pack*

14
15 318 Participants will be provided with a survey pack containing the following questionnaires:

- 16
17 319 (1) Integrated Palliative Outcome Scale (I-POS-Renal): a validated questionnaire measuring the
18
19 320 presence and severity of disease related symptoms. The I-POS-Renal was developed based on
20
21 321 the POS and IPOS palliative care surveys, but with the additional inclusion of symptoms
22
23 322 common in CKD such as pruritus and restless legs.⁷⁶
- 24 323 (2) 12-Item Short Form Health Survey (SF-12): a validated 12-item questionnaire used to assess
25
26 324 generic health outcomes from the patient's perspective.⁷⁷
- 27 325 (3) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): a validated 13-item
28
29 326 multidimensional scale that assesses fatigue over the past seven days using a 5-point Likert
30
31 327 scale that covers physical fatigue, functional fatigue, emotional fatigue, and social
32
33 328 consequences of fatigue with excellent internal consistency and test-retest reliability.^{78 79}
- 34 329 (4) Pittsburgh Sleep Quality Index (PSQI): self-rated questionnaire which assesses sleep quality
35
36 330 and disturbances over a 1-month time interval.⁸⁰
- 37 331 (5) Patient Activation Measure (PAM): a validated, licenced tool measuring the spectrum of
38
39 332 knowledge, skills, and confidence in patients and capturing the extent to which they feel
40
41 333 engaged and confident in taking care of their condition ('activation').⁸¹
- 42 334 (6) Brief Health Literacy Screen (BHLS): a 3-item questionnaire to identify inadequate health
43
44 335 literacy,⁸² validated against longer screening tools in populations with ESKD.^{83 84}
- 45 336 (7) The Global Physical Activity Questionnaire (GPAQ): developed by the World Health
46
47 337 Organisation (WHO) for physical activity surveillance in countries. It collects information on
48
49 338 physical activity participation in three settings or domains (activity at work, travel to and from
50
51 339 places, and recreational activities) as well as sedentary behaviour, comprising 16 questions.⁸⁵
- 52 340 (8) Duke Activity Status Index (DASI): a 12-item questionnaire that uses self-reported physical
53
54 341 work capacity to estimate peak metabolic equivalents and has been shown to be a valid
55
56 342 measurement of functional capacity.⁸⁶

57
58 343 *Habitual physical activity*
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3 344 Objective data on habitual physical activity levels over a 7-day period (ideal minimum 6-days)⁸⁷ will be
4
5 345 gained from tri-axial accelerometers (GENEActiv, ActivInsights Ltd., Cambridge, UK). Participants will
6
7 346 receive the monitor at the baseline and follow-up assessments and will be asked to wear it from
8
9 347 midnight that evening for 7 days.

10 348 *Blood and urine sampling*

11
12 349 Venous blood (30 ml) will be collected using venepuncture of the antecubital vein and prepared and
13
14 350 stored appropriately for the following analysis:

- 15
16 351 • Circulating markers of cardiovascular disease
- 17
18 352 • Circulating markers of systemic inflammation and oxidative stress
- 19
20 353 • Blood glucose and HbA1c
- 21
22 354 • Lipids and triglycerides
- 23
24 355 • Full blood count and renal profile

25
26 356 A urine sample will be requested to ascertain urinary protein:creatinine ratio.

27 28 357 **Follow-up assessments**

29
30 358 Follow up visits are summarised in Figure 1. An instructional session (or more if required) following
31
32 359 baseline assessments will allow the intervention group to become familiar with the exercise
33
34 360 requirements and allow the research team to ensure safety and competence before commencing the
35
36 361 12-week home-based training program. This can be via video call or in-person. At 6 weeks into the 12-
37
38 362 week period for the intervention group only, participants will be invited to review exercise progression
39
40 363 (via video call or in-person), particularly if participants are struggling to undertake the requisite
41
42 364 amount of exercise, and as a refresher of the intervention. This combined with regular contact from
43
44 365 research staff should aid participant compliance and monitoring.

45
46 366 Final assessments will be conducted for the exercise and control groups within 7 days of completing
47
48 367 the 12-week exercise or control period. Assessments completed will be identical to the baseline visit
49
50 368 with the addition of a 'patient satisfaction questionnaire' to allow pragmatic future development of
51
52 369 the study. This will also be offered to participants who withdraw from the trial. Three months after
53
54 370 completing the exercise intervention, participants will be contacted for a semi-structured one-to-one
55
56 371 telephone interview. This will aim to understand the impact of the intervention, if any, on subsequent
57
58 372 lifestyle and exercise habits.

59 60 373 **Sub-studies**

61
62 374 Additional informed consent will be sought for:

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2
3 375 1. Ten 'healthy' control participants to undertake a CPET to assess the differences, if any,
4 376 between CPET parameters in 'healthy controls' versus KTRs, particularly during the recovery
5 377 period.
6
7
8 378 2. KTRs completing the exercise intervention will be invited to undertake a semi-structured
9 interview (via telephone, video call, or in-person) incorporating exercise self-efficacy,
10 379 enjoyment, difficulties encountered, perceived advantages and disadvantages of the
11 380 intervention, and study design. Participants who withdraw before the end of the intervention
12 381 will also be invited to attend, although in line with ethical standards, this will be optional.
13 382
14
15
16

17 383 **Sample size**

18
19 384 The purpose of this pilot study is to obtain appropriate data to adequately power future definitive
20 385 trials;⁸⁸ a power calculation is neither relevant nor possible. A minimum sample size of 50 is based on
21 386 accepted values to provide adequate estimates of standard deviations for future power calculations.⁸⁹
22
23
24

25 387 **Data collection and management**

26
27 388 Data from all time points will be collected in case report forms (CRFs) by the trial team. All data will
28 389 be entered into a secure database and will only be accessible on password-protected computers at
29 390 UHL and University of Leicester by relevant members of the study team. No identifying information
30 391 will be kept in electronic form. All source data and original participant identities will be kept in a locked
31 392 office in the trial site file only at UHL.
32
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36 393 **Data analysis**

37
38 394 Data will be assessed for normality using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous
39 395 data to be expressed as mean (\pm standard deviation), if normally distributed or median (interquartile
40 396 range) if not. To investigate the differences between interventions we will use analysis of (co-) variance.
41 397 Independent samples t-tests and Mann-Whitney U tests will be used to assess for baseline
42 398 differences between variables for normally and non-normally distributed data respectively. These
43 399 data will be used to inform the power calculation for future definitive trials.
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48 400 Qualitative data will be transcribed verbatim and analysed according to the principles of interpretive
49 401 thematic analysis to explore themes emerging from patient journeys through, and experiences of, the
50 402 interventions and outcome measures.
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53

54 403 Outcomes pertaining to the feasibility of the intervention and trial will be assessed and include:

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56 404
 - *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.
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3 407 • *Adherence to the exercise intervention*: the number of completed sessions per week and
4 specific intensity and durations achieved.
5 408
6
7 409 • *Acceptability of randomisation*: comparison of the final group characteristics and
8 identification of any stratification variables, if applicable.
9 410
10 411 • *Attrition rate*: the number of participants that drop-out of the study.
11
12 412 • *Outcome acceptability*: the percentage of missing data for each outcome measure.
13
14 413 • *Safety*: The number of self-reported injuries or adverse events throughout the trial.

15
16 414 The *a priori* thresholds for specific feasibility and acceptability criteria are as follows: eligibility ($\geq 50\%$),
17 415 recruitment success of 20% of eligible participants (≥ 2 participants per month), adherence (an average
18 416 of 3 exercise sessions per week) and attrition ($\leq 30\%$).

417 **Safety reporting**

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

422 An SAE is any AE that:

- 423 • is life threatening
424 • requires hospitalization or prolongation of a hospital admission
425 • results in a persistent or significant disability/incapacity
426 • is a congenital anomaly
427 • results in death

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

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

436 **Patient and public involvement**

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

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2
3 440 with PPI partners who advised on intervention content and outcome measure acceptability, paying
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5 441 particular attention to patient burden, ensuring outcome measures would not over-burden
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7 442 participants. The PPI group approved the final design and duration of this intervention and advised
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9 443 the inclusion of an initial supervised intervention familiarisation period to build confidence in exercise
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11 444 capability.

12 445 **Changes to the study protocol following the COVID-19 pandemic**

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14 446 The COVID-19 pandemic has made us all review the ways we design and deliver clinical studies. Whilst
15
16 447 patient safety remains the absolute priority of clinical and research teams, there is a need for research
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18 448 to continue in a safe way that balances the benefits of continuing programs of research against the
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20 449 risks from COVID-19. We have amended the study protocol in several ways to reduce any additional
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22 450 exposure of patients to clinical environments where COVID-19 may be present:

- 23 451 • We have reduced the number of study visits to a minimum. The original study flow diagram is
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25 452 included in Additional file 1. All interim assessments have been removed in the modified
26
27 453 protocol (Fig. 1) and the baseline and final study visits are now wrapped into part of patient
28
29 454 clinical care. That is to say, when they attend for their baseline and follow-up study visits they
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31 455 will have their clinical review and clinical blood tests as they would for their normal clinical
32
33 456 care with a transplant nephrologist (MGB), so there is no increase in-patient visits to a clinical
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35 457 environment over-and-above their normal care.
- 35 458 • The original study design included a 2-week face-to-face training period where participants
36
37 459 would attend the hospital to learn how to complete the exercises and the exercise program
38
39 460 with a member of the research team. This training period will now be done remotely, via video
40
41 461 conferencing, with discussion and feedback over the telephone and using the instructional
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43 462 videos and literature that support the home-based exercise intervention.
- 43 463 • When participants attend for their study visits, departmental procedures have been updated
44
45 464 to now include meticulous cleaning of all equipment before and after use, one-way flows of
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47 465 participants to ensure participants do not mix, and the use of personal protective equipment
48
49 466 for all staff and participants.

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51 467 The above changes have been agreed with the local REC and the study sponsor and have allowed
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53 468 recommencement of study recruitment and procedures.

54 469 **DISCUSSION**

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57 470 This pilot study is designed to assess the feasibility of delivering a structured, home-based, exercise
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59 471 intervention in KTRs at increased cardiometabolic risk and evaluate the putative effects on
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472 cardiovascular structure and functional changes, cardiorespiratory fitness, quality of life, healthcare

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3 473 utilisation, patient activation, and engagement with the prescribed exercise program. It is the first trial
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5 474 to use a pragmatic home-based program of exercise this patient group. It is also the first to use CMR
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7 475 to evaluate the structural and functional changes of the heart in this at risk population.

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9 476 Qualitative data will provide valuable personal perspectives on the acceptability of this specific
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11 477 exercise program. Transplant recipients experience complex medical journeys and are likely to have
12
13 478 specific unmet needs in the area of exercise and lifestyle.⁹⁰ This will be valuable information for future
14
15 479 randomised controlled trials (RCTs) and exercise guideline development.

16 480 Home-based intervention outcomes are reliant on accurate reporting by participants with regards to
17
18 481 frequency, intensity, and duration of exercise performed. This under-reporting is often a limitation of
19
20 482 unsupervised interventions. We will ensure participants are correctly advised of how to monitor and
21
22 483 report their exercise completion throughout the trial and encourage this through telephone
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24 484 communications.

25 485 We anticipate that a positive outcome will lead to both an increased understanding of the specific
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27 486 exercise requirements of KTRs and the development of new programs that promote longer-term
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29 487 engendered lifestyle change that can be incorporated into standard practice with much lower financial
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31 488 implications than in-centre supervised rehabilitation.

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492 ETHICS AND DISSEMINATION

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494 Ethical issues

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496 University of Leicester are the sponsor for this study (UOL 0714). The protocol was reviewed by the
497 East Midlands-Nottingham 2 research ethics committee and was given a favourable opinion (REC ref
498 19/EM/0209) on 14/10/2019. Health Research Authority regulatory approval was given on
499 14/10/2019, and the study was adopted on the National Institute for Health Research (NIHR) portfolio
500 on 26/09/2019. Local governance approval was granted by UHL R&I on 31/01/2020. This study was
501 prospectively registered with ClinicalTrials.gov (NCT04123951; 11.10.2019). The first participant was
502 recruited on 09/03/2020. The predicted study end date is 31/12/2022. This manuscript is quorate with
503 the most recent approved protocol (version 6 26.08.2020). Relevant parties will be informed of any
504 substantial protocol modifications. Steps have been taken when designing this protocol to minimise
505 the ethical implications and ensure patient welfare. The study will comply with the International
506 Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research
507 Governance Framework for Health and Social Care.

508

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

517

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

519

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

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6
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8
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16 533
17
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19
20 535
21 536 **Consent for publication:** Not applicable.

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25 538 **Figure Caption:**

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28 539 Figure 1. ECSERT study flow diagram

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Table 1. ECSERT inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
RTRs	
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Diabetes mellitus • Dyslipidaemia • Hypertension • Obesity (BMI >30) • History of ischaemic heart disease/cerebrovascular disease 	<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • Age <18 years • No documented history of major cardiorespiratory chronic condition • None of the following cardiometabolic risk factors: <ul style="list-style-type: none"> • Diabetes mellitus • Dyslipidaemia • Hypertension • History of ischaemic heart disease/cerebrovascular disease • Obesity (BMI>30) • Not on any medication 	<ul style="list-style-type: none"> • 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 \geq 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.

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809 **Additional file details**

810 File name: Additional File 1

811 File format: Additional File 1.pdf

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

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

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For peer review only

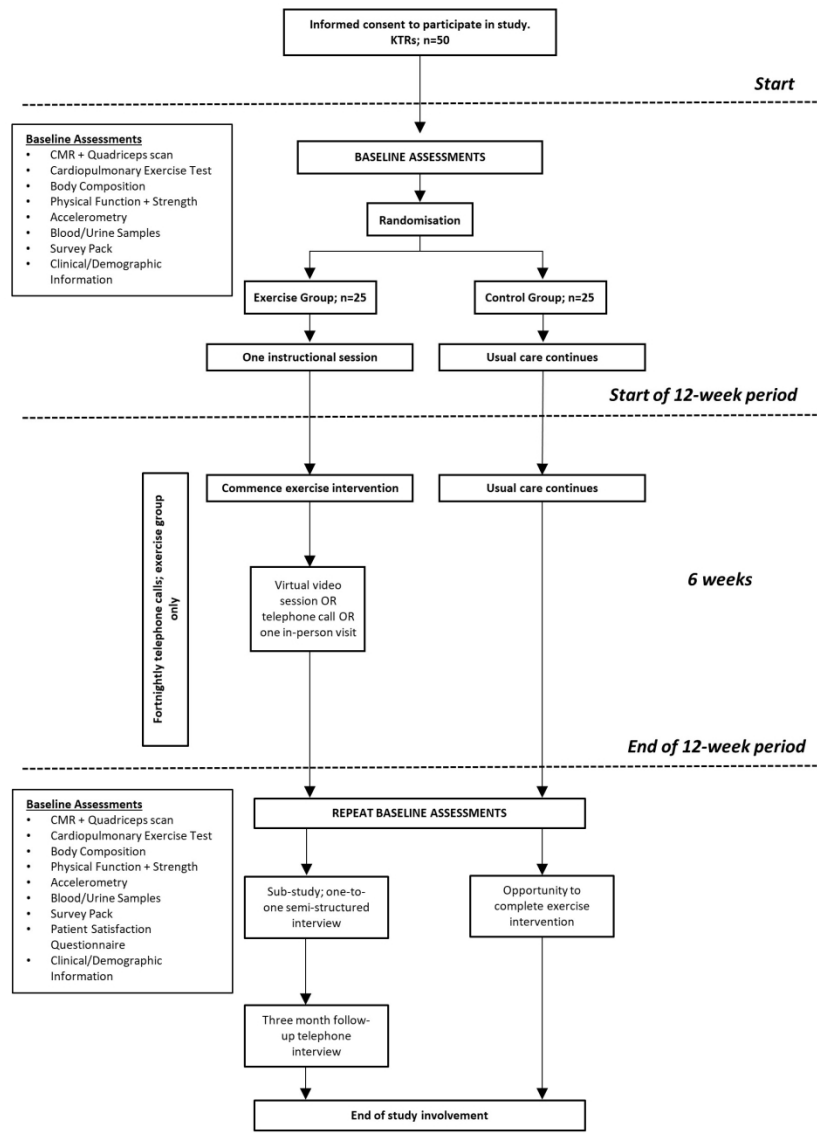


Figure 1 ECSERT Study Flow Diagram

170x219mm (300 x 300 DPI)

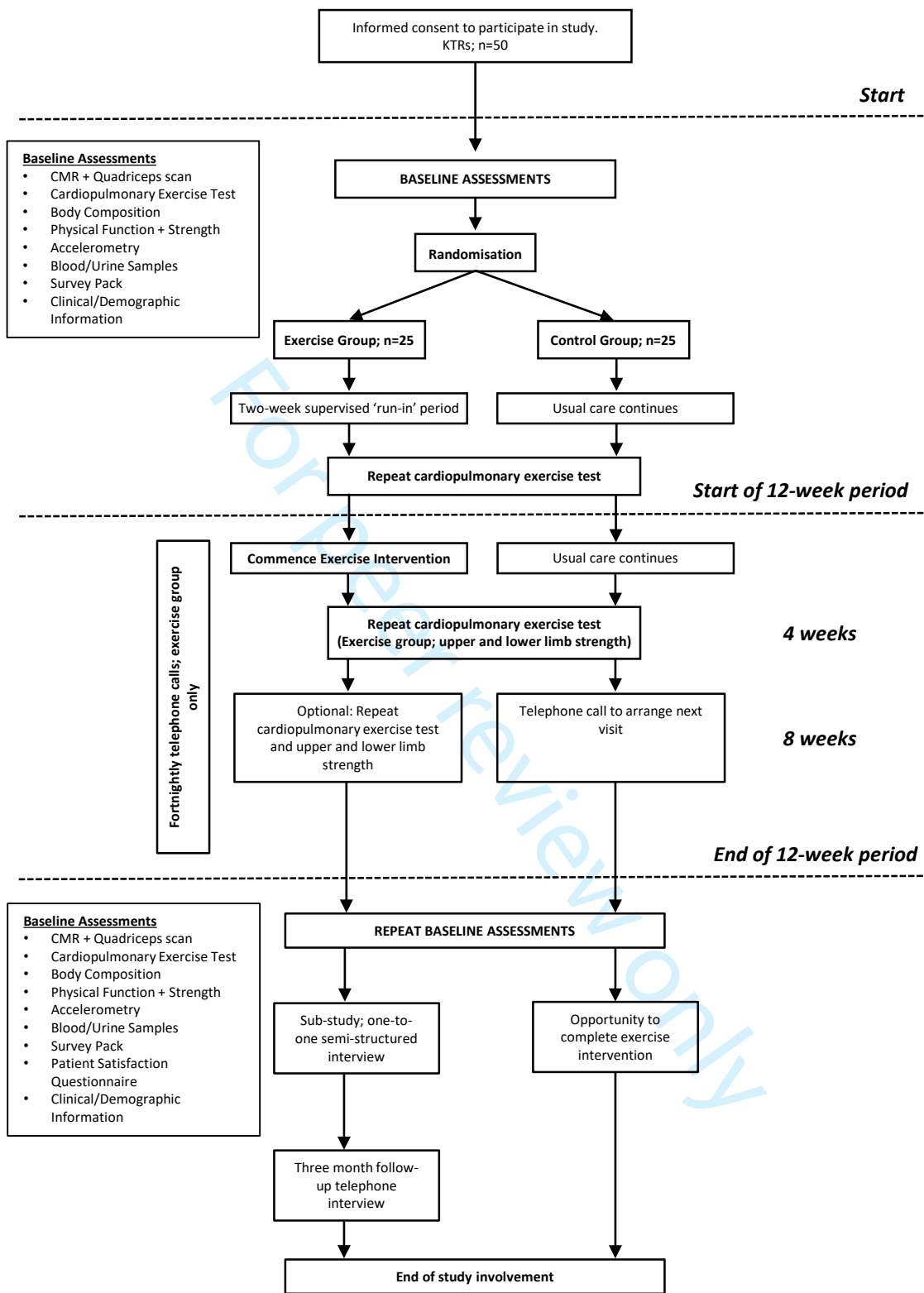


Figure X. Original ECSERT study flow diagram (pre-COVID-19)



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)

1			
2	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)
3			
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8	Methods: Participants, interventions, and outcomes		
9			
10	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)
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14	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)
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 5 and 6)
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22		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)
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28		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)
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32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 5, line 164)
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35	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)
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43	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)
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48	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)
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54	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 5, 140+)
55			
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2 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)

10 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)

16 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Page 5, 158)

20 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A

25 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A

29 **Methods: Data collection, management, and analysis**

31 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)

39 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)

44 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)

52 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)

56 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A

1
2 20c Definition of analysis population relating to protocol non-adherence
3 (eg, as randomised analysis), and any statistical methods to handle
4 missing data (eg, multiple imputation) (Page 12)
5

6 **Methods: Monitoring**
7

8 Data monitoring 21a Composition of data monitoring committee (DMC) or Data and Safety
9 Monitoring Board (DCMB); summary of its role and reporting
10 structure; statement of whether it is independent from the sponsor
11 and competing interests; and reference to where further details about
12 its charter can be found, if not in the protocol. Alternatively, an
13 explanation of why a DMC is not needed
14
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16
17 A DSMB is indicated, from a practical perspective in the following
18 circumstances:
19

- 20
21 1. If the trial is intended to provide definitive information about
22 effectiveness and/or safety of a medical or bio-behavioral intervention
23 2. If there are prior data to suggest that the intervention being studied has
24 the potential to induce potentially unacceptable toxicity
25 3. If the trial is evaluating mortality or another major endpoint, such that
26 inferiority of one treatment arm has safety as well as effectiveness
27 implications
28 4. If it would ethically be important for the trial to stop early if the primary
29 question addressed has been definitively answered, even if secondary
30 questions or complete safety information were not yet fully addressed
31

32 The ECSERT study does not meet any of these criteria as a pilot/feasibility
33 study
34

35 21b Description of any interim analyses and stopping guidelines,
36 including who will have access to these interim results and make the
37 final decision to terminate the trial N/A
38

39
40 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
41 spontaneously reported adverse events and other unintended effects
42 of trial interventions or trial conduct (Page 12, safety reporting)
43

44 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
45 whether the process will be independent from investigators and the
46 sponsor N/A aside from usual sponsor audits
47
48

49 **Ethics and dissemination**
50

51 Research ethics 24 Plans for seeking research ethics committee/institutional review
52 approval board (REC/IRB) approval (Page 16, ethical issues)
53

54 Protocol 25 Plans for communicating important protocol modifications (eg,
55 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
56 (eg, investigators, REC/IRBs, trial participants, trial registries,
57 journals, regulators) (Page 16, ethical issues)
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2	Consent or	26a	Who will obtain informed consent or assent from potential trial
3	assent		participants or authorised surrogates, and how (see Item 32) (page 5)
4			
5		26b	Additional consent provisions for collection and use of participant
6			data and biological specimens in ancillary studies, if applicable
7			(consent form)
8			
9	Confidentiality	27	How personal information about potential and enrolled participants
10			will be collected, shared, and maintained in order to protect
11			confidentiality before, during, and after the trial (Page 11)
12			
13	Declaration of	28	Financial and other competing interests for principal investigators for
14	interests		the overall trial and each study site (Page 16, line 515)
15			
16	Access to data	29	Statement of who will have access to the final trial dataset, and
17			disclosure of contractual agreements that limit such access for
18			investigators (Page 17, availability of data)
19			
20			
21	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
22	post-trial care		compensation to those who suffer harm from trial participation N/A
23			
24	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
25	policy		participants, healthcare professionals, the public, and other relevant
26			groups (eg, via publication, reporting in results databases, or other
27			data sharing arrangements), including any publication restrictions
28			(Page 17, availability of data)
29			
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32		31b	Authorship eligibility guidelines and any intended use of professional
33			writers (Page 17, availability of data)
34			
35		31c	Plans, if any, for granting public access to the full protocol,
36			participant-level dataset, and statistical code (Page 17, availability of
37			data)
38			
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40	Appendices		
41			
42	Informed consent	32	Model consent form and other related documentation given to
43	materials		participants and authorised surrogates Yes
44			
45	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
46	specimens		specimens for genetic or molecular analysis in the current trial and
47			for future use in ancillary studies, if applicable (Page 10)
48			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.