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Exercise for people living with frailty and receiving haemodialysis: a mixed-methods randomised controlled feasibility study.

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4 1 **Exercise for people living with frailty and receiving haemodialysis: a mixed-**
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3 41 **ABSTRACT**
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6 42 **Objectives**
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9 43 Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This
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11 44 study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic
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13 45 exercise is feasible for frail HD patients, and explore how the intervention may be tailored to
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16 46 their needs.
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19 47 **Design**
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22 48 Mixed-methods feasibility.
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25 49 **Setting & participants**
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28 50 Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7
29
30 51 (vulnerable to severely frail) were eligible for the feasibility study.
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33 52 **Interventions**
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36 53 Participants in the exercise group undertook six-months of thrice-weekly, progressive,
37
38 54 moderate intensity intradialytic cycling (IDC).
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41 55 **Outcomes**
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44 56 Primary outcomes were related to feasibility. Secondary outcomes were falls incidence,
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46 57 exercise capacity, physical function, physical activity and patient-reported outcomes
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48 58 (PROMS) at baseline and six months. Acceptability of trial procedures and the intervention
49
50 59 were explored via diaries and interviews with n=25 frail HD patients who both participated in
51
52 60 (n=13, 52%), and declined (n=12, 48%), the trial.
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56 61 **Results**
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3 62 124 (31%) patients were eligible, 64 (52%) consented and 51 (80%) completed a baseline
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5 63 assessment. N=24 (71% male; 59 ± 13 years) dialysed during shifts randomly assigned to
6
7 64 exercise and n=27 (81% male; 65 ± 11) assigned to usual care. N=6 (12%) were lost to
8
9 65 follow-up. The exercise group completed 74% of sessions. 27 to 89% of secondary outcome
10
11 66 data were missing. Frail HD patients outlined several ways to enhance trial procedures.
12
13 67 Maintaining ability to undertake activities of daily living and social participation were
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15 68 outcomes of primary importance. Participants desired a varied exercise programme.
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20 69 **Conclusions**

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23 70 A definitive RCT is feasible, however a comprehensive exercise programme may be more
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25 71 efficacious than IDC in this population.
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28 72 **Trial Registration**

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31 73 ISRCTN11299707; ISRCTN12840463
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38 75 **Keywords:** feasibility; frailty; exercise; haemodialysis; mixed-methods.
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76 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 77 • To our knowledge, this is the first study to evaluate the feasibility of an exercise
78 intervention for people living with frailty and receiving haemodialysis (HD).
- 79 • The Clinical Frailty Scale, a frailty risk-stratification measure which has been
80 validated in an HD population, was used to identify eligible participants.
- 81 • This study is also the first to explore how trial procedures and exercise programmes
82 should be specifically tailored to the needs of people living with frailty and receiving
83 HD, from their own perspectives.
- 84 • Multiple qualitative methods (interviews and diaries) were used to explore
85 participants perceptions, providing a form of triangulation which strengthens the
86 conclusions made.
- 87 • Due to the nature of the intervention and resource limitations, we could not blind
88 intervention providers, outcome assessors or study participants to group allocation.

89 INTRODUCTION

90 Frailty, “a multidimensional syndrome of decreased physiological reserve leading to
91 increased vulnerability to minor health stressors”, is highly prevalent within the
92 haemodialysis (HD) population^{1,2}. Increasing frailty is associated with worsening outcomes,
93 including mortality, hospitalisation, falls, reduced Health-Related Quality of Life (HRQoL),
94 psychological well-being, physical function, ability to undertake activities of daily living
95 (ADLs) and increased symptom burden³⁻⁵.

96
97 Despite this, frailty is not static and evidence suggests that some factors associated with
98 frailty are amenable to change⁶. Whilst the possible mediating role of exercise has been
99 discussed, to our knowledge no original studies have examined the feasibility or effectiveness
100 of an exercise programme for people living with frailty and receiving HD⁷. To date, exercise
101 interventions for HD patients have focused upon intradialytic exercise, most commonly
102 delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about
103 whether this is the most appropriate training stimulus for frail HD patients⁸. In addition, HD
104 treatment can be poorly tolerated by frail patients and therefore IDC may represent an
105 additional stressor to which these patients are particularly vulnerable⁹. European renal best
106 practice guidance highlights a need for studies which identify how exercise programmes
107 should be more specifically tailored to the needs of frail CKD patients¹⁰, yet to date, there has
108 also been no exploration of the needs, barriers and facilitators to exercise from the
109 perspectives of people living with frailty and receiving HD themselves.

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111 The aim of this study was to determine the feasibility of conducting an RCT investigating the
112 effects of IDC for HD patients living with frailty by: (i) estimating rates of eligibility,

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3 113 recruitment, retention, exercise adherence and outcome acceptability; and exploring (ii) the
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5 114 potential benefits of IDC across a range of secondary outcomes; and (iii) the perceptions of
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8 115 frail HD patients in relation to participating in clinical research, IDC and a tailored exercise
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10 116 intervention.

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14 15 16 118 **METHODS**

17 18 19 119 **Design**

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22 120 A mixed-methods, prospective, randomised feasibility study was conducted alongside
23
24 121 concurrent qualitative diaries and interviews (Trial Registration numbers ISRCTN11299707;
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26 122 ISRCTN12840463). The feasibility study was a secondary analysis of the *CYCLE-HD* trial,
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29 123 whose aims and methods are reported elsewhere¹¹. The qualitative component was
30
31 124 underpinned by a constructivist Grounded Theory approach¹². All participants provided
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33 125 written informed consent.

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37 38 39 127 **Participants**

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42 128 Prevalent adult (over 18 years) HD patients were recruited from three centres within the UK
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44 129 East Midlands Renal Network. In addition to the inclusion and exclusion criteria for the
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47 130 *CYCLE-HD* trial (supplementary material 1), the Clinical Frailty Scale (CFS), a risk
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49 131 stratification tool validated in a HD population, was used to identify vulnerable to severely
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51 132 frail participants (CFS score 4-7)¹³. The inclusion and exclusion criteria for the qualitative
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54 133 component mirrored the feasibility study and both those involved in the trial, and those who
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56 134 were eligible but declined to participate were eligible.

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3 136 **Randomisation**
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6 137 HD cohorts were randomised prior to screening, based on a computer-generated
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8 138 randomisation algorithm held by the Robertson Centre for Biostatistics at the University of
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10 139 Glasgow.
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16 141 **Recruitment**
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19 142 Patients were screened for eligibility by their supervising nephrologist. Suitable patients were
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21 143 approached during HD, and the study explained. For the qualitative component, participants
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23 144 who had been involved in the feasibility study were recruited following completion of, or
24
25 145 withdrawal from, the trial to prevent contamination.
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32 147 **Exercise intervention**
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35 148 Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance¹⁴.
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37 149 Briefly, following a one-month run-in, participants in the exercise group undertook thrice-
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39 150 weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC
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41 151 (MOTomed Letto2, Reck, Germany), for six months¹⁵. Cycling resistance was progressively
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43 152 increased to maintain RPE in response to exercise adaptation. Both arms continued with usual
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45 153 care HD as described elsewhere¹¹.
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52 155 **Sample size**
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55 156 Determinations of sample size from a power calculation around a primary outcome are not
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57 157 relevant to a feasibility study and sample sizes of 24-50 are considered sufficient¹⁶. For the
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3 158 qualitative component maximum variation sampling was initially used to ensure diversity in
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5 159 frailty status and level of trial participation¹². As understanding was gained from preliminary
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7 160 analyses, theoretical sampling was used to further recruit participants¹². A maximum of 30
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9 161 interviews were planned, but data collection ceased at the point where theoretical categories
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11 162 were saturated and no longer generated new insight (n=25).
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164 **Primary outcome measures**

165 The primary feasibility outcomes are presented in supplementary material 3. Judgement
166 regarding feasibility was based upon a set of *a priori* progression criteria. For each criterion,
167 the development of ‘stop’ (indicating when there are issues with the trial that cannot be
168 resolved) and ‘go’ thresholds (when there are no issues that may impede the success of a
169 trial) were co-produced by patients, clinicians and researchers^{17,18}. Results falling between
170 these thresholds indicated that adaptation to trial procedures may render a definitive RCT
171 viable¹⁸.
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173 **Baseline demographic and clinical variables**

174 Demographic and clinical characteristics were gathered from participants’ medical notes. The
175 Charlson Comorbidity Index (CCI) was used to estimate the burden of comorbid disease¹⁹.
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177 **Secondary outcome measures**

178 Multiple secondary outcomes were used to determine the potential effects of IDC and most
179 appropriate primary endpoint for a future RCT. Outcome assessors were not blinded to group
180 allocation.

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6 182 Information on the number of falls, defined as ‘an unexpected event in which the participants
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8 183 come to rest on the ground, floor, or lower-level’ which resulted in Emergency Department
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10 184 visits and hospital admissions were collected from baseline to one year following intervention
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13 185 completion from medical records and hospital episode statistics²⁰.

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19 187 Field tests of exercise capacity and physical function included the Incremental Shuttle Walk
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21 188 Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance
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23 189 Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60)¹¹. Physical activity (PA) was
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25 190 objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc.,
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27 191 Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were
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29 192 used to ensure representative data for average daily wear-time, steps per day, and time
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31 193 (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS)
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33 194 moderate (3-6 METS) and vigorous (>6 METS) PA²¹. PROMs collected are outlined in
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35 195 supplementary material 4¹¹. All outcomes were collected at baseline and six months.

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43 197 Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as
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45 198 outlined previously¹¹.

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50 51 200 **Diaries and interviews**

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54 201 Participants first completed a prospective falls diary, recognised as the current ‘gold
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56 202 standard’ for falls data collection, for up to three months to examine the feasibility of this
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58 203 outcome measure within a future definitive RCT²⁰. Semi-structured interviews then explored
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3 204 participants' experiences of: (i) keeping a falls diary; (ii) participating in a trial; and (iii) their
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5 205 perceptions of IDC and a tailored exercise intervention.
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11 207 Information to support diary collection and a topic guide for the interviews (supplementary
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13 208 material 5) was developed by HMLY, HE and a patient and public involvement group.
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15 209 Topics were tailored according to the level of involvement in the trial, and the content of
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17 210 diaries. Interviews were conducted during HD, in the participant's home, or in the hospital by
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19 211 HMLY and lasted 20 to 120 minutes (mean 63 minutes). All were digitally audio-recorded
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21 212 and transcribed verbatim.
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28 214 **Data analysis**

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31 215 Descriptive statistics and confidence intervals were used to estimate feasibility outcomes²³.
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33 216 The percentage of exercise sessions completed was used to establish the acceptability of IDC.
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35 217 Outcome acceptability was determined by quantifying the amount of missing data across
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37 218 secondary outcomes. No imputation was performed to account for missing data. No statistical
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39 219 testing relating to the efficacy of the exercise intervention was undertaken, although the
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41 220 potential benefits of exercise were estimated²³. For falls, incident rate ratio and 95%
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43 221 confidence intervals were presented. Statistical analyses were performed using SPSS 24
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45 222 (IBM UK Ltd, UK).
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53 224 Qualitative analysis was undertaken by HMLY and SG and informed by a constant
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55 225 comparative approach¹². Transcripts were reviewed, then coded line by line, followed by
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57 226 focused, and then theoretical, coding¹². NVivo11 software (QSR International Ltd, version
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3 227 11, 2016) was used to facilitate data management. Finally, qualitative and quantitative results
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5 228 were merged in a 'joint display' to facilitate an overall assessment of feasibility²⁴.
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10 11 230 **Patient and public involvement**

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14 231 The patient and public involvement (PPI) group for this study comprised patients of all ages,
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16 232 genders and ethnicities who were living with frailty and receiving HD, and their relatives.
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18 233 They agreed this study was an important priority for further investigation and particularly
19
20 234 stressed the need to add the qualitative component. The PPI group were involved early in
21
22 235 ethical approval stages and were actively engaged in writing lay summaries and providing
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24 236 patient perspectives on data collection procedures, ethical issues, and the study dissemination
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26 237 plans. They assisted in the preparation of study documentation, interview topic guides and
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28 238 diary keeping materials. During the study, members of the PPI group attended regular
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30 239 steering meetings and were involved in co-producing the progression criteria.
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38 241 **RESULTS**

39 242 **Feasibility study**

40 243 *Eligibility and recruitment*

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44 244 Screening and recruitment took place from March 2015 to 2018, with data collection
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46 245 completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients
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48 246 screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as
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50 247 vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four
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52 248 participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of
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54 249 time or family support and reluctance to undergo outcome testing, or to be randomised.
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3 250 Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline assessment.

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5 251 N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four (47%)

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8 252 participants received dialysis during shifts randomised to exercise and twenty-seven (53%)

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10 253 during shifts randomised to usual care.

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16 255 *Participant characteristics*

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18 256 Table 1 displays the characteristics of the trial participants at baseline. Groups were well

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20 257 matched across most variables. A lower proportion of participants were female (23.5%) and

21
22 258 severely frail (6%) overall.

259 *Table 1. Baseline demographic and clinical characteristics of the trial participants.*

		Usual care (n=27)	Exercise (n=24)	All (n=51)
Age (years)		65 ± 11	59 ± 13	63 ± 12
Sex (n, %)	Female	5 (19%)	7 (29%)	12 (23.5%)
Ethnicity (n, %)	White	12 (44%)	11 (41%)	23 (45%)
	Asian or Asian British	11 (41%)	11 (46%)	22 (43%)
	Caribbean	1 (4%)	0 (0%)	1 (2%)
	Other ethnic	1 (4%)	1 (4%)	2 (4%)
	Not stated	2 (7%)	1 (4%)	3 (6%)
Diagnosis (n, %)	Aetiology Uncertain	8 (29%)	7 (29%)	15 (29%)
	Diabetic Nephropathy	5 (19%)	7 (29%)	12 (23%)
	Glomerulonephritis	5 (19%)	3 (14%)	8 (16%)
	Renal Vascular Disease	3 (11%)	2 (8%)	5 (10%)
	Other diagnoses	4 (15%)	1 (4%)	5 (10%)
	Chronic Pyelonephritis	2 (7%)	1 (4%)	3 (6%)
	Polycystic Kidney Disease	0 (0%)	2 (8%)	2 (4%)
	Not recorded	0 (0%)	1 (4%)	1 (2%)
CCI		5 ± 2	5 ± 2	5 ± 2
Previous transplant (n, %)	No	21 (75%)	18 (75%)	39 (76.5%)
	Yes	6 (21%)	6 (25%)	12 (23.5%)
Time on HD (months)		17 (7-53)	13 (10-61)	16 (8-53)
BMI (kg/m²)		27.38 ± 6.72	25.87 ± 5.28	26.67 ± 6.07
Total no. medications		12 ± 4	12 ± 4	12 ± 4
Clinical Information	Albumin (g/L)	35.4 ± 4.4	37.4 ± 4.3	36.4 ± 4.4
	Haemoglobin (g/L)	107 ± 12	112 ± 17	107 ± 15
Haemodialysis	URR (%)*	74 (70-80)	75 (58-79)	74 (71-79)
	SBP (mmHg)	143 ± 21	144 ± 21	144 ± 21
	DBP (mmHg)*	65 (62-78)	78 (69-86)	76 (62-81)
CFS (n, %)	Vulnerable	13 (48%)	10 (42%)	23 (45%)
	Mildly frail	5 (18.5%)	7 (29%)	12 (23.5%)
	Moderately frail	8 (30%)	5 (21%)	13 (25.5%)
	Severely frail	1 (3.5%)	2 (8%)	3 (6%)

260 *Values reported are mean and SD (±), except for *median and IQR. Abbreviations: BMI, body mass*
 261 *index; CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale DBP, diastolic blood pressure;*
 262 *SBP, systolic blood pressure; URR, urea reduction ratio*

263 *Retention*

264 Six (12%, 95% CI 4.4% to 23.9%) participants were lost to follow-up: three participants
 265 withdrew due to ill-health, one moved away, one changed HD regime and one withdrew
 266 consent.

267

268 *Exercise adherence*

269 A mean of 61 ± 17 exercise sessions were completed over the six-month intervention,
 270 representing an adherence rate of $74 \pm 20\%$. The most frequent reasons for missing an exercise
 271 session were declining ($n= 175$ out of 535 sessions omitted in total, 33%), feeling unwell ($n=$
 272 116, 22%) and pain ($n= 105$, 20%). Table 2 summarises the mean amount of exercise
 273 achieved. On average, participants reached the prescribed level of exercise by six months,
 274 although $n=18$ (75%) were unable to achieve this by the end of the one-month run-in period.

275 *Table 2 Mean (SD) exercise achieved per session over the six-month duration of the*
 276 *intervention.*

Duration (mins)	35 ± 8
Speed (RPM)	63 ± 10
Intensity (RPE)	13 ± 1
Gear	9 ± 4
Distance (Miles)	7 ± 3
Power (Watts)	13 ± 6
Energy expenditure (Kcals)	64 ± 31

277 *All data presented as mean and SD (\pm). Abbreviations: kcals, kilocalories, mins, minutes; RPE, rating*
 278 *of perceived exertion; RPM, revolutions per minute.*

279

280 *Outcome acceptability*

281 For tests of exercise capacity (ISWT and ESWT); $n=14$ (27%) did not complete at least one
 282 test at baseline, $n=30$ (64%) at interim and $n=26$ (58%) at final. For tests of physical function;
 283 $n=20$ (39%) did not complete at least one test at baseline, $n=33$ (70%) at interim and $n=30$
 284 (67%) at final. For PROMs; $n=27$ (53%) did not complete at least one questionnaire at

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3 285 baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were
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5 286 missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the
6
7 287 primary reason for non-completion for all outcomes across all time points.
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14 289 *Secondary outcomes*

15
16 290 Summary falls data are presented in supplementary material 6. The crude falls incident rate
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18 291 ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased
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20 292 incidence of falls within the usual care group.
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26 294 Exercise capacity was maintained in the exercise group, but deteriorated in the usual care
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28 295 group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181
29
30 296 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also
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32 297 increased in the usual care group (suggesting a deterioration in function), but was maintained
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34 298 in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15)
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36 299 (supplementary material 7).
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44 301 Step count increased in the exercise group by 859 steps/day (95%CI -825 to 2543) on HD
45
46 302 days and 888 steps/day (95%CI -84 to 1861) on non-HD days. Whilst sedentary time was
47
48 303 increased in the exercise group on all days compared with the usual care group, this appeared
49
50 304 to be offset by increases in light PA and moderate PA, and maintenance (albeit of low levels)
51
52 305 of vigorous PA versus maintenance or deterioration across the same metrics in the usual care
53
54 306 group (supplementary material 8). For PROMs, outcomes were largely unchanged, except for
55
56 307 the DASI score, which appeared to deteriorate in the exercise group and increase in the usual
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58 308 care group, resulting in an overall difference in score of 4.93 (95% CI -0.94 to 10.80) and the
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3 309 mental component summary score of the SF12 which improved in the usual care group,
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5 310 resulting in an overall difference in score of 4 (95% CI -3 to 10). Exercisers appeared to have
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8 311 a greater perception of the benefits of exercise compared with those in the control group (3,
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10 312 95% CI -4 to 11) (supplementary material 9).

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16 314 *Serious adverse events*

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18 315 In total, n=13 (25%) experienced an SAE during the feasibility study, n=8 (33%) in the
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20 316 exercise group and n=5 (19%) in the usual care group. All events resolved, and none were
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22
23 317 directly related to the intervention or trial.

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29 319 **Qualitative findings**

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32 320 Thirty-seven patients were approached for the qualitative study. Twenty-six were recruited
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34 321 and one died prior to data collection. Thirteen had participated in the feasibility trial. Nine
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36 322 received dialysis during shifts randomised to exercise, and four randomised to usual care.
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38 323 Twelve participants had declined to take part in the feasibility trial. Full characteristics for the
39
40 324 qualitative sample are provided in supplementary material 10.

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47 326 In addition to categories relating to the feasibility outcomes, categories relating to both the
48
49 327 delivery and the characteristics of a tailored exercise intervention were identified. These are
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51 328 presented alongside illustrative quotes within Tables 3, 4, 5 and 6 and Figure 2.

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3 330 *Feasibility and acceptability of a definitive trial*
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6 331 *Eligibility and recruitment*
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8 332 Declining to participate was underpinned by a perception that the trial could worsen overall
9
10 333 health, particularly amongst those who had not previously participated in research or had
11
12 334 recently commenced HD. Female participants believed that exercise was predominantly for
13
14 335 men and that they were already doing enough daily activity, whilst participants living with
15
16 336 moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by
17
18 337 exercise. Motivators included a sense of altruism, and the perception that participation could
19
20 338 provide opportunities to improve individual outcomes; learn about their own health; and
21
22 339 access better healthcare. Participants felt that recruitment could be enhanced by the effective
23
24 340 use of non-verbal communication, rapport building, and actively involving family members
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26 341 in the recruitment process, as family support was often a prerequisite to participation (Table
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28 342 3).
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37 344 *Trial retention*
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39 345 The primary reasons for withdrawal were becoming unwell, the duration of the trial and the
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41 346 research not meeting participants expectations. Participants suggested that having a rapport
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43 347 and maintaining regular dialogue with the research team might help retain participants within
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45 348 a future trial (Table 3).
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349 *Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative*
350 *quotes.*

For peer review only

1
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3 351 *The acceptability of IDC*
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5 352 IDC was generally perceived to be a safe and positive use of HD treatment time. However,
6
7 353 IDC was described as limited in scope, and participants were uncertain of its impact,
8
9
10 354 particularly upon mobility, symptoms and falls (Table 4).
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16 356 *Table 4. Categories relating to the acceptability of IDC outcome acceptability and*
17 357 *illustrative quotes.*
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22 359 *Outcome acceptability*
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24 360 As indicated by participant quotations in Table 5, the number of outcomes and follow-ups
25
26 361 needed to be reduced and participants had a strong preference for outcomes that could be
27
28 362 collected during HD treatment. Many found the ISWT and STS60 assessments too
29
30 363 challenging. Participants were occasionally uncertain of the purpose of the questionnaires and
31
32 364 many reported difficulty quantifying symptom severity or a desire to provide ‘anticipated’
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34 365 responses.
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42 367 Maintaining mobility, and the ability to undertake a range of ADLS and social roles were
43
44 368 viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative
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46 369 study agreed to complete a falls diary and many reported they preferred falls information to
47
48 370 be collected during HD treatment. The majority who had fallen rarely reported them to
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50 371 healthcare professionals, believing that they were an expected consequence of HD or having
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52 372 had experience of their concerns about falls being overlooked. Consequently, falls prevention
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54 373 was not viewed as a key outcome.
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374 *Table 5. Categories relating to outcome acceptability and illustrative quotes.*

For peer review only

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3 375 *Perceptions of a tailored exercise programme*
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6 376 *Delivery*
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8 377 There was no universally acceptable setting for exercise delivery (Table 6). Vulnerable and
9
10 378 mildly frail participants (CFS 4-5) were particularly open to group-based exercise in the
11
12 379 community or gym, which they felt would provide motivation through camaraderie with
13
14 380 others. However, access barriers due to HD treatment, complex health needs, and lack of
15
16 381 transport were common. Participants also described feeling self-conscious exercising
17
18 382 amongst 'normal' people. Home-based exercise was preferred by those with moderate to
19
20 383 severe frailty (CFS 6-7) due to easier access, greater flexibility and relevance to their daily
21
22 384 activities. Despite this, concerns about lack of space and safety were highlighted by those
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24 385 who lived alone, whilst those with family were concerned about overburdening or injuring
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26 386 them by asking for support.
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387 *Table 6. Participants perceptions of the facilitators and barriers to group and home-based exercise.*

For peer review only

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3 388 *Characteristics of a tailored exercise programme*
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5 389 Irrespective of the setting for delivery, participants identified several key features of a
6
7 390 tailored exercise intervention which are summarised in Figure 2.
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13 392 *Preparation*
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16 393 Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and
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18 394 dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts
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20 395 of exercise (for example breathlessness whilst exercising) were interpreted as worsening
21
22 396 symptoms or damage, and many participants were uncertain if exercise would be suitable or
23
24 397 beneficial. They indicated that the reason for exercising needed to be sufficiently compelling.
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26 398 They wanted to know what to expect prior to exercising, and individualised goal setting was
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28 399 advocated to build motivation and appreciate improvements.
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33 401 *Content*
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36 402 Key components described were whole body resistance, aerobic and balance training. Many
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38 403 participants described being unable to get up once they had fallen and felt that practising this
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40 404 was also important. Routine physical activity was viewed as more purposeful than structured
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42 405 exercise ‘for the sake of it’ and participants spoke of their enjoyment of being outside and
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44 406 engaging in meaningful and physically active hobbies.
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53 408 *Structure*
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55 409 Supervision was viewed as essential to select, teach and progress exercises. Individual
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57 410 tailoring which considered the impact of disability, comorbidities and fluctuating symptoms
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59 411 was important, and a choice of exercises, for example swimming, dancing and yoga, was
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3 412 associated with increased enjoyment and engagement. Moderate to severely frail participants
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5 413 wanted the programme to be progressed in a supportive and collaborative manner. Those who
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7 414 were vulnerable or mildly frail wanted to be 'pushed' and progressed in a more assertive
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9 415 manner.

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16 417 Having a companion (typically peers, family or friends) was viewed as helping to overcome
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18 418 access barriers and provide socialisation and mutual motivation. The sharing of experience
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20 419 was also seen as a powerful means of challenging preconceptions about exercise ability,
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22 420 although participants with moderate to severe frailty raised concerns about feeling
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24 421 embarrassed or 'judged' if they were less able.

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29 30 31 423 **Integrated mixed-methods analyses**

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34 424 The integrated qualitative and quantitative findings suggest that an RCT of IDC is feasible for
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36 425 frail HD patients following adaptation. However, IDC should not be the only intervention
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38 426 offered and the development of a multicomponent programme is warranted (Supplementary
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40 427 material 11).

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45 46 47 429 **DISCUSSION**

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50 430 These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to
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52 431 increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was
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54 432 viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest
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56 433 that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity,
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58 434 endurance and functional muscle strength and increase PA behaviour (steps/day). Despite
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3 435 this, participants described a preference for a multi-component programme that prepared
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5 436 them for exercise, offered variety, companionship and individualised supervision. No single
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7 437 preferred environment for the delivery of this intervention was identified but appeared to be
8
9 438 influenced by frailty grade and individual factors.
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16 440 27% to 89% of secondary outcome measure data were missing, and, overall, this progression
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18 441 criterion was not achieved. Given that secondary measures are often insufficiently powered,
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20 442 reducing the number collected within a future trial may improve completion²⁷. Falls were not
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22 443 of primary importance to participants, and aligns with the SONG-HD data which did not
23
24 444 identify falls as a key outcome²⁹. Our findings suggest that accurately capturing prospective
25
26 445 falls data may be challenging due to under-reporting, and yet, retrospective falls data
27
28 446 collection does not fully reflect the incidence and impact of falls. Given the high incidence of
29
30 447 falls in this population, capturing falls data may be important in a future trial, and researcher-
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32 448 led prospective data collection at the dialysis unit is recommended, in line with participant
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34 449 feedback⁵. Further exploration and validation of meaningful measures for HD patients living
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36 450 with frailty is also warranted. Some of the functional measures (the STS60 and ISWT)
37
38 451 included were too challenging and measures of independence, rarely used in exercise studies
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40 452 to date, were highlighted as important within this study, and have also been included in
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42 453 guidelines and core outcomes sets for HD and older people²⁸⁻³⁰.
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52 455 The results of this study indicate that changes to eligibility criteria and screening are required.
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54 456 As only patient participants were interviewed, it was not possible to gain any insight on this
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56 457 aspect of feasibility from the qualitative component. Importantly, the challenges of
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58 458 identifying eligible participants do not appear to be unique to this study. Studies of older
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3 459 people living with frailty highlight that large numbers need to be screened to achieve a 50%
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5 460 recruitment rate, and a multicentre trial may be required²⁷.
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11 462 This study suggests that IDC may reduce falls incidence in frail HD patients potentially by
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13 463 attenuating a decline in exercise capacity, physical activity behaviour and function at levels
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15 464 shown to be clinically meaningful in other long-term conditions^{31,32}. This indicates that
16
17 465 preventing deterioration may be as valuable, and more attainable, as improving outcomes in a
18
19 466 frail population. Despite this, frail participants experienced difficulties achieving the
20
21 467 proposed level of exercise and maintaining motivation in the face of varying symptomology.
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23 468 Exercise programmes have a dose-response, and these factors may have reduced participants
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25 469 physical capability to exercise and achieve optimal benefit, despite the overall good level of
26
27 470 adherence. Clinical decision support tools have been used in other populations to rationalise
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29 471 exercise prescription, progression and amendment in the presence of varying symptomology,
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31 472 and a similar approach may be beneficial for frail HD patients³³.
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40 474 This study indicates that participants desire a multicomponent exercise programme, and
41
42 475 require an intervention that addresses their particularly low levels of PA. Whilst step count
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44 476 and time spent in light and moderate PA increased following IDC, these were below PA
45
46 477 recommendations for older people³⁴. To date, PA interventions for HD patients have
47
48 478 predominantly centred around walking, which may not be appropriate for those living with
49
50 479 frailty³⁵⁻³⁸. This study suggests that functional training (task-orientated exercises which
51
52 480 engages multiple muscle groups) and physical activity that focuses on 'doing more' of these
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54 481 usual tasks may be more acceptable and efficacious. To date, two studies have employed
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56 482 similar approaches with non-frail HD patients. One study demonstrated significant
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3 483 improvements in lower extremity performance and the other a non-significant improvement
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5 484 in physical function and maintenance of other SF-36 domains compared with the control
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8 485 group^{39,40}. In older people without CKD who are living with frailty, functional training
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10 486 included as part of a multicomponent exercise programme is beneficial across a range of
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12 487 outcomes, including greater ability to rise from the floor following a fall ^{38,41-44}. A similar
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14 488 approach to exercise prescription may be warranted in a frail HD population.

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20 490 Numerous barriers and facilitators to exercise were identified within this study, which have
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22 491 implications for the design of a programme. The use of theory is crucial in the development
23
24 492 of effective interventions and the behaviour change wheel (BCW) is most frequently cited in
25
26 493 the development of interventions in CKD⁴⁵. Mapping the identified barriers and facilitators to
27
28 494 the BCW indicates that ameliorating symptom burden prior to exercise, individualised
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30 495 exercise counselling, and a collaborative, problem-solving approach to exercise education are
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32 496 most likely to encourage and sustain participation^{45,46}. Devising ways in which peer and
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34 497 family involvement can be incorporated into the programme may also increase motivation
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36 498 and opportunity to exercise but should be carefully managed given the potential for negative
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38 499 comparison amongst the frailest patients.

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44 501 A lack of preferred environment for intervention delivery may have implications for a
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46 502 definitive RCT. Exercise interventions require motivation, and limited engagement may
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48 503 negatively influence a trials external and internal validity. Ignoring patient preference is also
49
50 504 out of step with clinical practice, where rehabilitation involves shared decision-making.
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52 505 Taken together, these factors have implications for determining treatment effects and future
53
54 506 intervention implementation⁴⁷. There is increasing recognition that novel trial designs may be

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3 507 indicated when evaluating complex interventions and a Partially Randomised Patient
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5 508 Preference Trial, where participants without preference are randomised whilst those with a
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7 509 preference receive their choice, would provide information on both the efficacy of the
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9 510 intervention and the influence of preference^{47,48}.

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16 512 **Strengths and limitations**

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19 513 To our knowledge, this study is the first to examine the feasibility of an RCT of IDC for frail
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21 514 HD patients and to explore how trial procedures and exercise programmes should be
22
23 515 specifically tailored to the needs of this group, from their own perspectives.

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26 516 Key strengths were the use of a validated frailty risk-stratification measure and multiple
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28 517 qualitative methods which provided a form of triangulation⁴⁹. There were, however,
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30 518 challenges to recruiting severely frail participants to both the trial and the qualitative arms.
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32 519 Additionally, the views of clinicians and researchers were not explored. A future RCT should
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34 520 also blind outcome assessors to group allocation to reduce the potential for detection bias.
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41 522 **Conclusion**

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44 523 In summary, this study suggests that a future definitive trial of IDC is feasible within a HD
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46 524 population with a CFS of 4-7 and paying particular attention in the design to those factors
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48 525 mentioned above may facilitate improved rates of eligibility and outcome completion.
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50 526 Outcomes focusing on independence and participation should be the primary outcomes of
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52 527 interest in a future trial. Whilst an exploratory analysis suggests some potential benefits to
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54 528 IDC, a tailored intervention comprising a comprehensive multi-component programme,
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3 529 symptom management, education and behaviour change is better suited to frail HD patients'
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5 530 needs.
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12

13
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15
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18 535 statistical expertise.
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24 537 **COMPETING INTERESTS**
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26
27 538 The authors have no conflicts of interest to declare.
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34

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57 550 **AUTHORS CONTRIBUTIONS**
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2
3 551 Literature search: HMLY; Research idea and study design: HMLY, JOB; participant
4
5 552 recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC,
6
7 553 MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical
8
9 554 analysis: HMLY; supervision and mentorship: SC, HE, SG, SJS, ACS, JOB; manuscript
10
11 555 preparation: HMLY; reviewed final manuscript: all. Each author contributed important
12
13 556 intellectual content during manuscript drafting or revision and accepts accountability for the
14
15 557 overall work by ensuring that questions pertaining to the accuracy or integrity of any portion
16
17 558 of the work are appropriately investigated and resolved. All authors have read and approved
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19 559 the final version
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30 561 **ETHICAL APPROVAL**

31 562 This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and
32
33 563 South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial
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35 564 and the qualitative component respectively
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41 566 **DATA SHARING STATEMENT**

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44 567 The datasets used and analysed during the current study are available from the corresponding
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46 568 author on reasonable request.
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53 693 **LEGENDS TO FIGURES**

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56 694 Figure 1.CONSORT
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3 695 Figure 2. The core components of an acceptable exercise programme for people living with
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5 696 frailty and receiving haemodialysis.
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11 698 **SUPPLEMENTARY MATERIAL**
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14 699 Supplementary material 1. Inclusion and exclusion criteria for the CYCLE-HD trial
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17 700 Supplementary material 2. Summary of intervention characteristics, in line with TiDier
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19 701 guidance.
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22 702 Supplementary material 3. *A priori* progression criteria based on the primary feasibility
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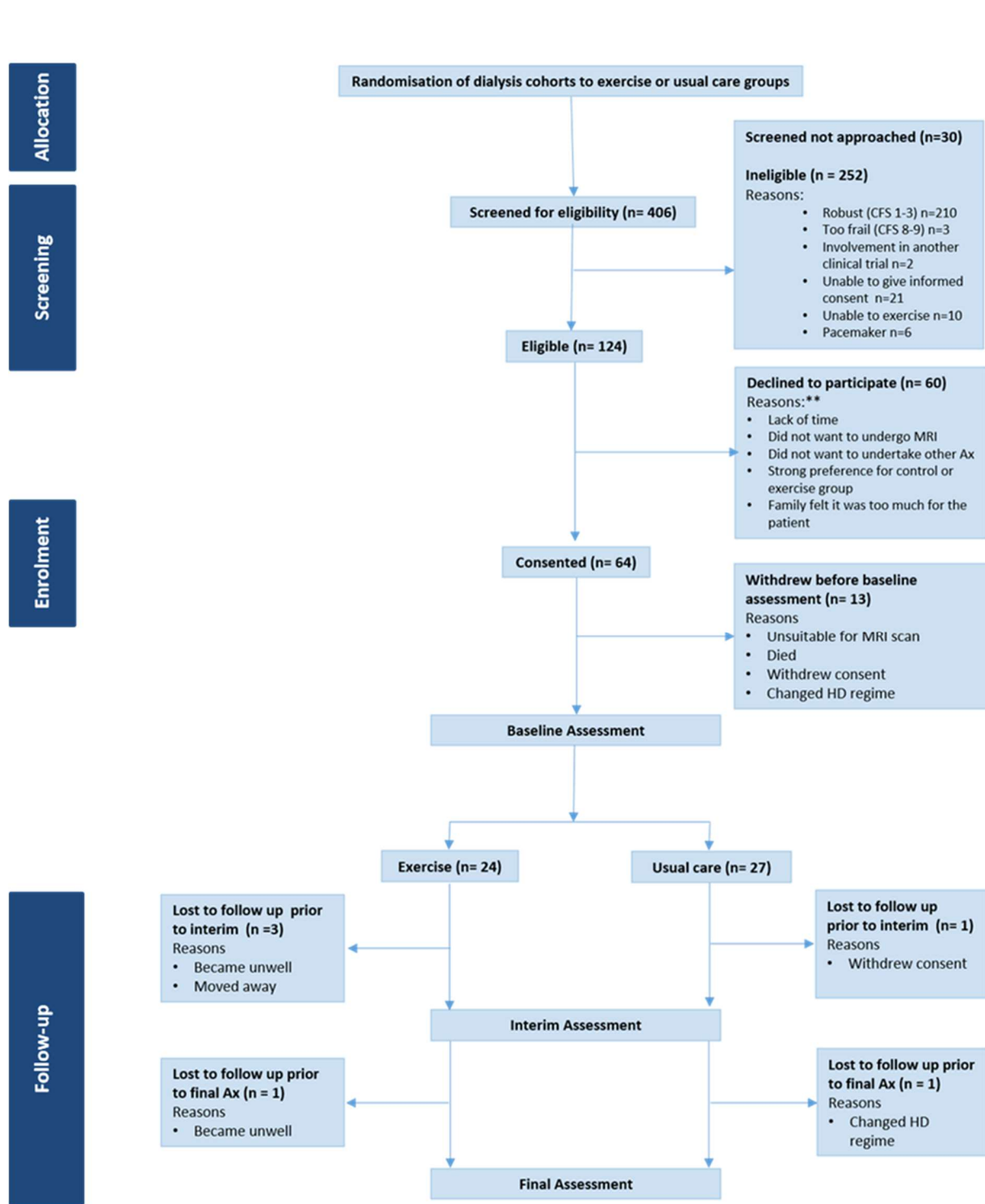
37 707 Supplementary material 7. Changes in exercise capacity and physical function after six
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50 712 qualitative participants.
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53 713 Supplementary material 11. Joint display of quantitative and qualitative results, with an
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55 714 overall assessment of mixed-methods inferences.
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Abbreviations: Ax, assessment; CFS, Clinical Frailty Scale; HD, haemodialysis.

Supplementary material 1. Inclusion and exclusion criteria for the *CYCLE-HD* trial.

Inclusion criteria	Exclusion criteria
Prevalent HD patient (> three months)	Unable to participate in current exercise programme due to perceived physical or psychological barriers
Aged 18 years or older	Unable to undergo MRI scanning (metal implants, severe claustrophobia)
Able and willing to give informed consent	Unfit to undertake exercise according to the American College of Sports Medicine (ACSM) guidelines

Supplementary material 2. Summary of intervention characteristics, in line with TiDier guidance.

Description of intervention.		A structured, supervised cycling exercise intervention delivered during in-centre HD.
Rationale.		<ul style="list-style-type: none"> • IDC aerobic and low-level resistance training, IDC is associated with increased adherence and is most widely used within practice.
What.	Materials provided to participants or used to support intervention delivery.	<ul style="list-style-type: none"> • Cycling was delivered using the Moto Med Letto 2 (Medimotion Ltd). • Materials: individualised exercise prescription and records of individual training bouts (duration (mins), intensity (RPE), resistance (gear), power output (watts) and energy expenditure (Kcal). • General information on the benefits of exercise (posters and leaflets) available across all 3 HD centres.
	Materials used to train intervention providers.	Standardised progression and training protocol used by all providers.
Who (intervention providers).		<ul style="list-style-type: none"> • Qualified exercise professionals with experience of delivering exercise to renal patients. • All providers were directly involved in the study, and not delivering the sessions as part of a clinical role. • Roles included exercise provision, supervision, monitoring and progression.
How (mode of delivery).		One to one, face to face.
Where (location).		Three HD units across the East Midlands, UK.
When and how much	The frequency of delivery.	Thrice weekly during each dialysis session.
	Target intensity of each bout of exercise.	RPE 12-14 (moderate intensity), cadence 60-70 RPM.
	Target duration of each bout of exercise.	At least 30 minutes of continuous exercise.
	The total duration of delivery.	Six months, with a one-month run-in period to achieve the target exercise prescription.
Tailoring.		<ul style="list-style-type: none"> • The starting resistance (gear) based on the individual's tolerance. • RPE used throughout to monitor and progress the exercise. • Interval training was permitted.

Abbreviations: HD, haemodialysis; Kcals, kilocalories; RPE, rating of perceived exertion, RPM, revolutions per minute.

Supplementary material 3. A priori progression criteria based on the primary feasibility objectives.

Eligibility	Stop	Less than 20% of all patients eligible
	Go	More than 50% of all patients eligible
Recruitment	Stop	Less than 25% of eligible patients recruited
	Go	More than 50% of eligible patients recruited
Exercise acceptability	Stop	Less than 30% adherence to the exercise sessions
	Go	More than 70% adherence to the exercise sessions
Outcome acceptability	Stop	Less than 70% outcome measure completion
	Go	More than 80% outcome measure completion
Loss to follow-up	Stop	More than 40% loss to follow-up
	Go	Less than 20% loss to follow-up

Supplementary material 4. Patient-reported secondary outcome measures.

Patient-reported secondary outcome	Construct measured
12-item Short-Form Health Survey Version 2 (SF-12)	Generic health-related quality of life. Higher scores reflect better HRQoL. Scores are presented as a mental and physical component summary score.
Palliative care Outcomes Scale – Renal version (POS-R)	Renal specific measure of symptomology and symptom burden. A global symptom score was calculated by totalling all the scored items within the questionnaire. The mean number of symptoms, symptom severity was also calculated. Higher scores reflect greater symptom burden.
Hospital Anxiety and Depression Scale (HADS)	Emotional distress. A score of ≥ 14 indicates the presence of emotional distress in HD patients
The Exercise Self-Efficacy Scale (ESES)	Exercise confidence. Higher scores reflecting greater self-efficacy.
Dialysis Patient-Perceived Exercise Benefits and Barriers Scale (DPPEBBS)	HD patients' perceptions of benefits and barriers to exercise. Higher scores indicate a greater perception of the benefits of exercise over barriers.
The Dukes Activity Status Index (DASI)	Self-reported physical function. Higher scores indicate higher levels of physical function. The questionnaire was also used to estimate VO_2 peak.

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3 *Supplementary material 5. Interview topic guide question.*
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5 Diary
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- 9 1. Can you tell me about how you have been using the diary?
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11 2. If we asked patients to keep diaries like yours as part of a future study, what might help
12 them?
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14 3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell
15 me more about...?
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19 Exercise intervention for frailty and falls
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23 4. For some people exercising helps to prevent falls, make people more able and feel better.
24 How do you feel about exercising?
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26 5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have
27 you seen these bikes?
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29 6. Programmes that are available for other people who fall include things like group exercise
30 and education. What do you think about this?
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32 7. These programmes usually take place at the hospital. What do you think about this?
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34 8. Some people prefer to do their exercise at home. What do you think about this?
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36 9. Where do you think a programme should be run?
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38 10. How often do you think you would be able to exercise?
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40 11. Would you want any support to help you exercise?
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42 12. What might put you off exercising?
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44 13. What questions might you have before you decide to take part or not?
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46 14. If you did take part in some kind of exercise programme, what improvements would you
47 most like to see?
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51 Research
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- 53 15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE
54 study (declined/ took part. If took part completed/dropped out) if patient unsure]
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56 16. What do you think about the information you receive when deciding to take part in a
57 research study?
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3 17. Often researchers ask you to complete some assessments or tests to see if the thing they
4 are studying is effective or not. What do you think would help patients to complete these
5 assessments/ tests?
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8 18. Sometimes people don't complete the research study, which may happen for several
9 reasons [give examples as needed]. What do you think would help keep dialysis from
10 dropping out of research studies?
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12 19. What would you like to happen once you reach the end of the study?
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For peer review only

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3 *Supplementary material 6. Incidence of falls per patient-year.*
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	Exercise	Usual care
Falls	5	11
Patient-year	36	40.5
Incidence rate	0.14	0.27

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Supplementary material 7. Changes in exercise capacity and physical function after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
ISWT (m)	n		16	15	36 (-12 to 84)
	Baseline		184 ± 130	237 ± 173	
	Final		158 ± 154	248 ± 192	
	Change		-26 ± 68	11 ± 63	
ESWT (secs)	n		14	15	181 (-92 to 453)
	Baseline		347 ± 384	401 ± 375	
	Final		193 ± 304	428 ± 423	
	Change		-153 ± 286	27 ± 413	
STS60 (n)	n		17	15	0 (-5 to 4)
	Baseline		10 ± 12	13 ± 11	
	Final		10 ± 13	13 ± 12	
	Change		0 ± 7	0 ± 6	
SPPB	Total score	n	17	15	0.5 (-0.7 to 2)
		Baseline	7 ± 3	9 ± 3	
		Final	6 ± 2	8 ± 3	
		Change	-1 ± 2	-0.5 ± 1	
	4m walk time (secs)	n	17	15	1 (-1 to 4)
		Baseline	7 ± 6	4 ± 1	
		Final	6 ± 4	5 ± 2	
		Change	1 ± 5	0 ± 1	
	Gait speed (m/s)	n	17	15	0.05 (-0.12 to 0.22)
		Baseline	0.74 ± 0.29	0.96 ± 0.28	
		Final	0.74 ± 0.28	0.91 ± 0.31	
		Change	0.00 ± 0.22	-0.05 ± 0.24	
	STS5 (secs)	n	9	10	5 (-4 to 15)
		Baseline	17 ± 7	16 ± 14	
		Final	23 ± 13	16 ± 10	
		Change	6 ± 11	0 ± 8	

Abbreviations: CI, confidence interval; ESWT, Endurance Shuttle Walk Test; ISWT, Incremental Shuttle Walk Test; m/s, metres per second; Secs, seconds; SPPB, Short Physical Performance Battery; STS5, Sit to Stand Five Repetitions; STS60, Sit to Stand in Sixty Seconds.

Supplementary material 8. Changes in physical activity (accelerometry data) after six months.

	Type of day		Usual Care	Exercise	Difference (95% CI)
Waking wear time (mins)	HD	n	5	10	244 (16 to 473)
		Baseline	891 ± 202	818 ± 183	
		Final	749 ± 105	921 ± 171	
		Change	-142 ± 166	103 ± 204	
	Non-HD	n	5	10	170 (-13 to 353)
		Baseline	893 ± 90	927 ± 216	
		Final	817 ± 134	1022 ± 165	
		Change	-75 ± 201	95 ± 129	
Steps (steps/day)	HD	n	5	10	859 (-825 to 2543)
		Baseline	2252 ± 4210	1373 ± 1080	
		Final	2464 ± 4783	2444 ± 1904	
		Change	211 ± 593	1070 ± 1665	
	Non-HD	n	5	10	888 (-84 to 1861)
		Baseline	3076 ± 5790	2387 ± 1696	
		Final	2645 ± 5284	2845 ± 2117	
		Change	-430 ± 603	458 ± 903	
Sedentary (mins/day)	HD	n	5	10	28 (-284 to 340)
		Baseline	954 ± 338	954 ± 203	
		Final	965 ± 208	992 ± 182	
		Change	10 ± 200	38 ± 287	
	Non-HD	n	5	10	124 (-205 to 454)
		Baseline	1022 ± 357	1103 ± 253	
		Final	912 ± 224	1117 ± 174	
		Change	-110 ± 298	14 ± 269	
Light PA (mins/day)	HD	n	5	10	91 (23 to -158)
		Baseline	125 ± 51	83 ± 42	
		Final	79 ± 39	127 ± 73	
		Change	-46 ± 45	44 ± 62	
	Non-HD	n	5	10	9 (-71 to 91)
		Baseline	145 ± 59	133 ± 50	
		Final	154 ± 99	151 ± 59	
		Change	9 ± 108	18 ± 44	
Moderate PA (mins/day)	HD	n	5	10	13 (-32 to 57)
		Baseline	83 ± 105	29 ± 33	
		Final	85 ± 123	43 ± 55	
		Change	1 ± 52	14 ± 29	
	Non-HD	n	5	10	20 (40 to -79)
		Baseline	79 ± 96	46 ± 61	
		Final	75 ± 112	62 ± 105	
		Change	-4 ± 40	16 ± 55	
Vigorous PA (mins/day)	HD	n	5	10	3 (-1 to 8)
		Baseline	4 ± 9	1 ± 1	
		Final	1 ± 2	1 ± 3	
		Change	-3 ± 7	0 ± 2	
	Non-HD	n	5	10	1 (0 to 2)
		Baseline	3 ± 0	1 ± 4	
		Final	2 ± 5	1 ± 4	
		Change	-1 ± 2	0 ± 0	

Abbreviations: CI, confidence interval; HD, haemodialysis; mins, minutes; PA, physical activity.

Supplementary material 9. Patient-reported outcomes measures after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
SF-12	PCS	n	19	19	0 (-4 to 5)
		Baseline	35 ± 9	35 ± 10	
		Final	36 ± 10	36 ± 10	
		Change	1 ± 7	1 ± 7	
	MCS	n	19	19	4 (-3 to 10)
		Baseline	43 ± 15	45 ± 13	
		Final	46 ± 13	45 ± 13	
		Change	4 ± 7	0 ± 12	
HADS	n	20	17	0 (-3 to 4)	
	Baseline	16 ± 10	15 ± 9		
	Final	14 ± 10	13 ± 9		
	Change	-2 ± 5	-2 ± 6		
POS-R	Global severity score	n	20	18	2 (-3 to 7)
		Baseline	19 ± 14	19 ± 14	
		Final	18 ± 14	20 ± 14	
		Change	1 ± 6	-1 ± 9	
	mean severity	n	20	18	0 (0 to 0)
		Baseline	2 ± 1	2 ± 1	
		Final	2 ± 1	2 ± 1	
		Change	0 ± 0	0 ± 0	
	mean number	n	22	16	0 (-1 to 2)
		Baseline	9 ± 4	10 ± 4	
		Final	9 ± 4	10 ± 5	
		Change	0 ± 4	0 ± 2	
ESES	n	19	16	0 (-1 to 1)	
	Baseline	2 ± 2	2 ± 1		
	Final	2 ± 1	2 ± 1		
	Change	0 ± 1	0 ± 1		
DPPEBBS	n	19	15	3 (-4 to 11)	
	Baseline	59 ± 10	59 ± 15		
	Final	61 ± 10	65 ± 7		
	Change	2 ± 7	6 ± 14		
DASI	n	20	18	4.93 (-0.94 to 10.80)	
	Baseline	13.06 ± 12.85	20.29 ± 14.33		
	Final	17.29 ± 14.41	19.60 ± 14.59		
	Change	4.22 ± 9.72	-0.71 ± 7.92		

Abbreviations: CI, confidence interval; DASI, Duke Activity Status Index; DPPEBBS, Dialysis Patients Benefits and Barriers Scale; ESES, Exercise Self efficacy Scale; HADS, Hospital Anxiety and Depression Scale; MCS, mental component summary score; POS-R, Palliative Outcomes Scale Renal, PCS, physical component summary score; VAS, visual analogue scale.

Supplementary material 10. Baseline demographic and clinical characteristics for the qualitative participants.

	N=25	
Age (years)	69±10	
Gender n (%)	Female	13 (52%)
	Male	12 (48%)
Ethnicity n (%)	White background	13 (52%)
	Asian or Asian British	10 (40%)
	Caribbean	1 (4%)
	Not stated	1 (4%)
Diagnosis	Diabetic nephropathy	11 (44%)
	Aetiology uncertain	6 (24%)
	Chronic pyelonephritis	3 (12%)
	Atypical hemolytic uremic syndrome	1 (4%)
	FSGS	1 (4%)
	Henoch-Schönlein Purpura	1 (4%)
	Minimal change nephropathy	1 (4%)
	Polycystic kidney disease	1 (4%)
CCI	6±2	
Time on HD (months)	43 (IQR 16-85)	
CFS n (%)	Vulnerable	9 (36%)
	Mildly frail	5 (20%)
	Moderately frail	8 (32%)
	Severely frail	3 (12%)
Number of falls in the last six months	3 (IQR 2-4)	
Previous transplant n (%)	No	21 (84%)
	Yes	4 (16%)
Active on transplant list n (%)	No	22 (88%)
	Yes	3 (12%)

Abbreviations: CCI, Charlson comorbidity index; CFS, clinical frailty scale; FSGS, Focal segmental glomerulosclerosis; HD, haemodialysis.

Supplementary material 11. Joint display of quantitative and qualitative results, with an overall assessment of mixed-methods inferences.

	Progression criteria	Feasibility trial	Qualitative results	Mixed-methods inferences
Eligibility	STOP <20% GO >50% eligible.	31% patients eligible	No discussion. Patients not involved in screening process	Silence
Recruitment	STOP <25% GO >50% recruited.	52% eligible patients recruited.	<ul style="list-style-type: none"> - Frailer and female participants less likely to be approached despite eligibility and have more concerns about the suitability - Perception that risks outweigh the potential benefit - Recruitment processes could be improved 	Complementary
Retention	STOP >40% GO <20% lost to follow-up.	12 % loss to follow-up. Reasons predominantly unavoidable (death, ill-health).	Loss to follow-up attributed to: <ul style="list-style-type: none"> - Illness; - length of trial; - the reality of being in the study not meeting expectations. 	Complementary
Intervention	STOP <30% GO >70% adherence over six-months.	74% adherence rate across the six-month exercise duration.	<ul style="list-style-type: none"> - IDC good use of time. - Participants felt safe and felt well supported. - IDC limited in scope. - Participants described a range of other important components 	Complementary
Outcome	STOP <70% GO >80% outcome measure completion.	Up to 89% of secondary outcome measure data missing Collection of falls data challenging.	<ul style="list-style-type: none"> - Number of outcomes measured to be reduced. - Outcome testing during HD or at home preferred. - 52% agreed to complete a falls diary, 12% lost. - STS60, ESWT and ISWT unsuitable - Researcher support and family involvement may increase completion - Outcomes measuring ADLs, participation and symptom prioritised 	Complementary Silence for PA monitoring.

Results from the feasibility trial are colour coded to depict whether they met the 'stop' (red), 'go' (green) or 'change (orange) progression criteria.

Abbreviations: ADLs, activities of daily living; ESWT, Endurance Shuttle Walk Test; IDC, intradialytic exercise; ISWT, Incremental Shuttle Walk Test; PA, physical activity; STS60, sit to stand in sixty seconds.



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6
	2b	Specific objectives or research questions for pilot trial	6-7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7 and supplementary material 1
	4b	Settings and locations where the data were collected	7-8,10-11
	4c	How participants were identified and consented	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8 and supplementary material 2
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9-11, supplementary materials 3,4 and 5
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	9 and supplementary material 3
Sample size	7a	Rationale for numbers in the pilot trial	8-9

	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	12-13 figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	12-13 figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 (trial) supplementary material 10 (qualitative)
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Supplementary materials 6-9 and page 15-17
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplementary materials 6-9 and page 15-17
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	17- 26
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P 17
	19a	If relevant, other important unintended consequences	n/a
Discussion			

1	Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	30
2	Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	26-31
3	Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	26-31
4		22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	26-31
5	Other information			
6	Registration	23	Registration number for pilot trial and name of trial registry	4 and 7
7	Protocol	24	Where the pilot trial protocol can be accessed, if available	7
8	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31
9		26	Ethical approval or approval by research review committee, confirmed with reference number	32

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15 Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. 2016;355.

16 *We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important
17 clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological
18 treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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BMJ Open

Exercise for people living with frailty and receiving haemodialysis: a mixed-methods randomised controlled feasibility study.

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine
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	REHABILITATION MEDICINE, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

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4 1 **Exercise for people living with frailty and receiving haemodialysis: a mixed-**
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7 2 **methods randomised controlled feasibility study.**
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3 41 **ABSTRACT**
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6 42 **Objectives**
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9 43 Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This
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11 44 study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic
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13 45 exercise is feasible for frail HD patients, and explore how the intervention may be tailored to
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16 46 their needs.
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19 47 **Design**
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22 48 Mixed-methods feasibility.
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25 49 **Setting & participants**
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28 50 Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7
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30 51 (vulnerable to severely frail) were eligible for the feasibility study.
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33 52 **Interventions**
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36 53 Participants in the exercise group undertook six-months of thrice-weekly, progressive,
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38 54 moderate intensity intradialytic cycling (IDC).
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41 55 **Outcomes**
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44 56 Primary outcomes were related to feasibility. Secondary outcomes were falls incidence,
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46 57 exercise capacity, physical function, physical activity and patient-reported outcomes
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48 58 (PROMS) at baseline and six months. Acceptability of trial procedures and the intervention
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50 59 were explored via diaries and interviews with n=25 frail HD patients who both participated in
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52 60 (n=13, 52%), and declined (n=12, 48%), the trial.
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56 61 **Results**
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3 62 124 (30%) patients were eligible, 64 (52%) consented and 51 (80%) completed a baseline
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5 63 assessment. N=24 (71% male; 59 ± 13 years) dialysed during shifts randomly assigned to
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7 64 exercise and n=27 (81% male; 65 ± 11 years) assigned to usual care. N=6 (12%) were lost to
8
9 65 follow-up. The exercise group completed 74% of sessions. 27 to 89% of secondary outcome
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11 66 data were missing. Frail HD patients outlined several ways to enhance trial procedures.
12
13 67 Maintaining ability to undertake activities of daily living and social participation were
14
15 68 outcomes of primary importance. Participants desired a varied exercise programme.
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20 69 **Conclusions**

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23 70 A definitive RCT is feasible, however a comprehensive exercise programme may be more
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25 71 efficacious than IDC in this population.
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28 72 **Trial Registration**

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31 73 ISRCTN11299707; ISRCTN12840463
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38 75 **Keywords:** feasibility; frailty; exercise; haemodialysis; mixed-methods.
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76 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 77 • To our knowledge, this is the first study to evaluate the feasibility of an exercise
78 intervention for people living with frailty and receiving haemodialysis (HD).
- 79 • The Clinical Frailty Scale, a frailty risk-stratification measure which has been
80 validated in an HD population, was used to identify eligible participants.
- 81 • This study is also the first to explore how trial procedures and exercise programmes
82 should be specifically tailored to the needs of people living with frailty and receiving
83 HD, from their own perspectives.
- 84 • Multiple qualitative methods (interviews and diaries) were used to explore
85 participants perceptions, providing a form of triangulation which strengthens the
86 conclusions made.
- 87 • Due to the nature of the intervention and resource limitations, we could not blind
88 intervention providers, outcome assessors or study participants to group allocation.

89 INTRODUCTION

90 Frailty, “a multidimensional syndrome of decreased physiological reserve leading to
91 increased vulnerability to minor health stressors”, is highly prevalent within the
92 haemodialysis (HD) population.^{1,2} Increasing frailty is associated with worsening outcomes,
93 including mortality, hospitalisation, falls, reduced Health-Related Quality of Life (HRQoL),
94 psychological well-being, physical function, ability to undertake activities of daily living
95 (ADLs) and increased symptom burden.³⁻⁵

96
97 Despite this, frailty is not static and evidence suggests that some factors associated with
98 frailty are amenable to change.⁶ Whilst the possible mediating role of exercise has been
99 discussed, to our knowledge no original studies have examined the feasibility or effectiveness
100 of an exercise programme for people living with frailty and receiving HD.⁷ To date, exercise
101 interventions for HD patients have focused upon intradialytic exercise, most commonly
102 delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about
103 whether this is the most appropriate training stimulus for frail HD patients.⁸ In addition, HD
104 treatment can be poorly tolerated by frail patients and therefore IDC may represent an
105 additional stressor to which these patients are particularly vulnerable.⁹ European renal best
106 practice guidance highlights a need for studies which identify how exercise programmes
107 should be more specifically tailored to the needs of frail CKD patients¹⁰, yet to date, there has
108 also been no exploration of the needs, barriers and facilitators to exercise from the
109 perspectives of people living with frailty and receiving HD themselves.

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111 The aim of this study was to determine the feasibility of conducting an RCT investigating the
112 effects of IDC for HD patients living with frailty by: (i) estimating rates of eligibility,

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3 113 recruitment, retention, exercise adherence and outcome acceptability; and exploring (ii) the
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5 114 potential benefits of IDC across a range of secondary outcomes; and (iii) the perceptions of
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8 115 frail HD patients in relation to participating in clinical research, IDC and a tailored exercise
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10 116 intervention.

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16 118 **METHODS**

19 119 **Design**

22 120 A mixed-methods, prospective, randomised feasibility study was conducted alongside
23
24 121 concurrent qualitative diaries and interviews (Trial Registration numbers ISRCTN11299707;
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26 122 ISRCTN12840463). The feasibility study was a secondary analysis of the *CYCLE-HD* trial,
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29 123 whose aims and methods are reported elsewhere.¹¹ The qualitative component was
30
31 124 underpinned by a constructivist Grounded Theory approach.¹² All participants provided
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33 125 written informed consent.

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39 127 **Participants**

42 128 Prevalent adult (over 18 years) HD patients were recruited from three centres within the UK
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44 129 East Midlands Renal Network. In addition to the inclusion and exclusion criteria for the
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47 130 *CYCLE-HD* trial (supplementary material 1), the Clinical Frailty Scale (CFS), a risk
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49 131 stratification tool, was used to identify vulnerable to severely frail participants (CFS score 4-
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51 132 7).¹³ The CFS has good predictive abilities in an HD population, good construct validity
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54 133 when compared with the Frailty Index, is less burdensome than the Frailty Phenotype, and has
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56 134 been validated in an HD population.¹³⁻¹⁵

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3 135 The inclusion and exclusion criteria for the qualitative component mirrored the feasibility
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5 136 study and both those involved in the trial, and those who were eligible but declined to
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7 137 participate, were eligible.
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12 13 14 139 **Randomisation**

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16 140 HD cohorts were randomised prior to screening, based on a computer-generated
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18 141 randomisation algorithm held by the Robertson Centre for Biostatistics at the University of
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20 142 Glasgow.
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25 26 27 144 **Recruitment**

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30 145 Patients were screened for eligibility by their supervising nephrologist. Suitable patients were
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32 146 approached during HD, and the study explained. For the qualitative component, participants
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34 147 who had been involved in the feasibility study were recruited following completion of, or
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36 148 withdrawal from, the trial to prevent contamination.
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41 42 43 150 **Exercise intervention**

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46 151 Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance.¹⁶
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48 152 Briefly, following a one-month run-in, participants in the exercise group undertook thrice-
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50 153 weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC
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52 154 (MOTomed Letto2, Reck, Germany), for six months.¹⁷ Cycling resistance was progressively
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54 155 increased to maintain RPE in response to exercise adaptation. Both arms continued with usual
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56 156 care HD as described elsewhere.¹¹
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158 Sample size

159 Determinations of sample size from a power calculation around a primary outcome are not
160 relevant to a feasibility study and sample sizes of 24-50 are considered sufficient.¹⁸ For the
161 qualitative component maximum variation sampling was initially used to ensure diversity in
162 frailty status and level of trial participation.¹² As understanding was gained from preliminary
163 analyses, theoretical sampling was used to further recruit participants.¹² A maximum of 30
164 interviews were planned, but data collection ceased at the point where theoretical categories
165 were saturated and no longer generated new insight (n=25).

166

167 Primary outcome measures

168 The primary feasibility outcomes are presented in supplementary material 3. Judgement
169 regarding feasibility was based upon a set of *a priori* progression criteria. For each criterion,
170 the development of ‘stop’ (indicating when there are issues with the trial that cannot be
171 resolved) and ‘go’ thresholds (when there are no issues that may impede the success of a
172 trial) were co-produced by patients, clinicians and researchers.^{19,20} Results falling between
173 these thresholds indicated that adaptation to trial procedures may render a definitive RCT
174 viable.²⁰

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176 Baseline demographic and clinical variables

177 Demographic and clinical characteristics were gathered from participants’ medical notes. The
178 Charlson Comorbidity Index (CCI) was used to estimate the burden of comorbid disease.²¹

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3 180 **Secondary outcome measures**
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6 181 Multiple secondary outcomes were used to determine the potential effects of IDC and most
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8 182 appropriate primary endpoint for a future RCT. Outcome assessors were not blinded to group
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10 allocation.
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16 185 Information on the number of falls, defined as ‘an unexpected event in which the participants
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18 186 come to rest on the ground, floor, or lower-level’ which resulted in Emergency Department
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20 187 visits and hospital admissions were collected from baseline to one year following intervention
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22 188 completion from medical records and hospital episode statistics.²²
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29 190 Field tests of exercise capacity and physical function included the Incremental Shuttle Walk
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31 191 Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance
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33 192 Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60).¹¹ Physical activity (PA) was
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35 193 objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc.,
36
37 194 Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were
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39 195 used to ensure representative data for average daily wear-time, steps per day, and time
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41 196 (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS)
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43 197 moderate (3-6 METS) and vigorous (>6 METS) PA.²³ PROMs collected are outlined in
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45 198 supplementary material 4.¹¹ All outcomes were collected at baseline and six months.
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54 200 Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as
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56 201 outlined previously.¹¹
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203 **Diaries and interviews**

204 Participants first completed a prospective falls diary, recognised as the current 'gold
205 standard' for falls data collection, for up to three months to examine the feasibility of this
206 outcome measure within a future definitive RCT.²² Semi-structured interviews then explored
207 participants' experiences of: (i) keeping a falls diary; (ii) participating in a trial; and (iii) their
208 perceptions of IDC and a tailored exercise intervention.

209
210 Information to support diary collection and a topic guide for the interviews (supplementary
211 material 5) was developed by HMLY, HE and a patient and public involvement group.
212 Topics were tailored according to the level of involvement in the trial, and the content of
213 diaries. Interviews were conducted during HD, in the participant's home, or in the hospital by
214 HMLY and lasted 20 to 120 minutes (mean 63 minutes). All were digitally audio-recorded
215 and transcribed verbatim.

217 **Data analysis**

218 Sample characteristics are presented as mean \pm standard deviation, median (IQR) or n (%), as
219 appropriate. Descriptive statistics and confidence intervals were used to estimate feasibility
220 outcomes.²⁴ The percentage of exercise sessions completed was used to establish the
221 acceptability of IDC. Outcome acceptability was determined by quantifying the amount of
222 missing data across secondary outcomes. No imputation was performed to account for
223 missing data. No statistical testing relating to the efficacy of the exercise intervention was
224 undertaken, although the potential benefits of exercise were estimated.²⁴ For falls, summary
225 data, incident rate ratio (the ratio of the incidence rate in the exercise group divided by the
226 incidence rate in the usual care group) and 95% confidence intervals were presented.

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3 227 Statistical analyses were performed using SPSS 24 (IBM UK Ltd, UK) and Stata 16
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5 228 (StataCorp LCC,USA).
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11 230 Qualitative analysis was undertaken by HMLY and SG and informed by a constant
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13 231 comparative approach.¹² Transcripts were reviewed, then coded line by line, followed by
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15 232 focused, and then theoretical, coding.¹² NVivo11 software (QSR International Ltd, version
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17 233 11, 2016) was used to facilitate data management. Finally, qualitative and quantitative results
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19 234 were merged in a ‘joint display’ to facilitate an overall assessment of feasibility.²⁵
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25 26 236 **Patient and public involvement**

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29 237 The patient and public involvement (PPI) group for this study comprised patients of all ages,
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31 238 genders and ethnicities who were living with frailty and receiving HD, and their relatives.
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33 239 They agreed this study was an important priority for further investigation and particularly
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35 240 stressed the need to add the qualitative component. The PPI group were involved early in
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37 241 ethical approval stages and were actively engaged in writing lay summaries and providing
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39 242 patient perspectives on data collection procedures, ethical issues, and the study dissemination
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41 243 plans. They assisted in the preparation of study documentation, interview topic guides and
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43 244 diary keeping materials. During the study, members of the PPI group attended regular
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47 245 steering meetings and were involved in co-producing the progression criteria.
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52 53 247 **RESULTS**

54 55 248 **Feasibility study** 56 57 58 59 60

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3 249 *Eligibility and recruitment*
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5 250 Screening and recruitment took place from March 2015 to 2018, with data collection
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8 251 completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients
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10 252 screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as
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12 253 vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four
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14 254 participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of
15
16 255 time or family support and reluctance to undergo outcome testing, or to be randomised. Those
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18 256 who declined to participate had a median age of 73 (IQR 67-8) years. N=35 (58%) were
19
20 257 female and n=27 (42%) male. Twenty-five (42%) were classified as vulnerable according to
21
22 258 the CFS, n=17 (28%) were mildly frail, n=9 (15%) moderately frail and n=9 (15%) severely
23
24 259 frail. Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline
25
26 260 assessment. N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four
27
28 261 (47%) participants received dialysis during shifts randomised to exercise and twenty-seven
29
30 262 (53%) during shifts randomised to usual care.
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39 264 [FIGURE ONE TRIAL CONSORT TO BE INSERTED HERE]
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45 266 *Participant characteristics*
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47 267 Table 1 displays the characteristics of the trial participants at baseline. Groups were well
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49 268 matched across most variables. A lower proportion of participants were female (23.5%) and
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51 269 severely frail (6%) overall.
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270 *Table 1. Baseline demographic and clinical characteristics of the trial participants.*

		Usual care (n=27)	Exercise (n=24)	All (n=51)
Age (years)		65 ± 11	59 ± 13	63 ± 12
Sex (n, %)	Female	5 (19%)	7 (29%)	12 (23.5%)
Ethnicity (n, %)	White	12 (44%)	11 (41%)	23 (45%)
	Asian or Asian British	11 (41%)	11 (46%)	22 (43%)
	Caribbean	1 (4%)	0 (0%)	1 (2%)
	Other ethnic	1 (4%)	1 (4%)	2 (4%)
	Not stated	2 (7%)	1 (4%)	3 (6%)
Diagnosis (n, %)	Aetiology Uncertain	8 (29%)	7 (29%)	15 (29%)
	Diabetic Nephropathy	5 (19%)	7 (29%)	12 (23%)
	Glomerulonephritis	5 (19%)	3 (14%)	8 (16%)
	Renal Vascular Disease	3 (11%)	2 (8%)	5 (10%)
	Other diagnoses	4 (15%)	1 (4%)	5 (10%)
	Chronic Pyelonephritis	2 (7%)	1 (4%)	3 (6%)
	Polycystic Kidney Disease	0 (0%)	2 (8%)	2 (4%)
	Not recorded	0 (0%)	1 (4%)	1 (2%)
CCI		5 ± 2	5 ± 2	5 ± 2
Previous transplant (n, %)	No	21 (75%)	18 (75%)	39 (76.5%)
	Yes	6 (21%)	6 (25%)	12 (23.5%)
Time on HD (months)		17 (7-53)	13 (10-61)	16 (8-53)
BMI (kg/m ²)		27.38 ± 6.72	25.87 ± 5.28	26.67 ± 6.07
Total no. medications		12 ± 4	12 ± 4	12 ± 4
Clinical Information	Albumin (g/L)	35.4 ± 4.4	37.4 ± 4.3	36.4 ± 4.4
	Haemoglobin (g/L)	107 ± 12	112 ± 17	107 ± 15
Haemodialysis	URR (%)*	74 (70-80)	75 (58-79)	74 (71-79)
	SBP (mmHg)	143 ± 21	144 ± 21	144 ± 21
	DBP (mmHg)*	65 (62-78)	78 (69-86)	76 (62-81)
CFS (n, %)	4, Vulnerable	13 (48%)	10 (42%)	23 (45%)
	5, Mildly frail	5 (18.5%)	7 (29%)	12 (23.5%)
	6, Moderately frail	8 (30%)	5 (21%)	13 (25.5%)
	7, Severely frail	1 (3.5%)	2 (8%)	3 (6%)

271 *Values reported are mean and SD (±), except for *median and IQR. Abbreviations: BMI, body mass*
 272 *index; CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale DBP, diastolic blood pressure;*
 273 *SBP, systolic blood pressure; URR, urea reduction ratio*

274 *Retention*

275 Six (12%, 95% CI 4.4% to 23.9%) participants were lost to follow-up: three participants
 276 withdrew due to ill-health, one moved away, one changed HD regime and one withdrew
 277 consent.

278

279 *Exercise adherence*

280 A mean of 61 ± 17 exercise sessions were completed over the six-month intervention,
 281 representing an adherence rate of $74 \pm 20\%$. The most frequent reasons for missing an exercise
 282 session were declining ($n = 175$ out of 535 sessions omitted in total, 33%), feeling unwell ($n =$
 283 116, 22%) and pain ($n = 105$, 20%). Table 2 summarises the mean amount of exercise
 284 achieved. On average, participants reached the prescribed level of exercise by six months,
 285 although $n = 18$ (75%) were unable to achieve this by the end of the one-month run-in period.

286 *Table 2 Mean (SD) exercise achieved per session over the six-month duration of the*
 287 *intervention.*

Duration (mins)	35 ± 8
Speed (RPM)	63 ± 10
Intensity (RPE)	13 ± 1
Gear	9 ± 4
Distance (Miles)	7 ± 3
Power (Watts)	13 ± 6
Energy expenditure (Kcals)	64 ± 31

288 *All data presented as mean and SD (\pm). Abbreviations: kcals, kilocalories, mins, minutes; RPE, rating*
 289 *of perceived exertion; RPM, revolutions per minute.*

290
 291 *Outcome acceptability*

292 For tests of exercise capacity (ISWT and ESWT); $n = 14$ (27%) did not complete at least one
 293 test at baseline, $n = 30$ (64%) at interim and $n = 26$ (58%) at final. For tests of physical function;
 294 $n = 20$ (39%) did not complete at least one test at baseline, $n = 33$ (70%) at interim and $n = 30$
 295 (67%) at final. For PROMs; $n = 27$ (53%) did not complete at least one questionnaire at

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2
3 296 baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were
4
5 297 missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the
6
7 298 primary reason for non-completion for all outcomes across all time points.
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13
14 300 *Secondary outcomes*

15
16 301 Summary falls data are presented in supplementary material 6. The crude falls incident rate
17
18 302 ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased
19
20 303 incidence of falls within the usual care group.
21
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24 304

25
26 305 Exercise capacity was maintained in the exercise group, but deteriorated in the usual care
27
28 306 group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181
29
30 307 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also
31
32 308 increased in the usual care group (suggesting a deterioration in function), but was maintained
33
34 309 in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15)
35
36 310 (supplementary material 7).
37
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44 312 Step count increased in the exercise group resulting in an overall difference of 859 steps/day
45
46 313 (95%CI -825 to 2543) on HD days and 888 steps/day (95%CI -84 to 1861) on non-HD days.
47
48 314 Whilst sedentary time was increased in the exercise group on all days compared with the
49
50 315 usual care group, this appeared to be offset by increases in light PA and moderate PA, and
51
52 316 maintenance (albeit of low levels) of vigorous PA versus maintenance or deterioration across
53
54 317 the same metrics in the usual care group (supplementary material 8). For PROMs, outcomes
55
56 318 were largely unchanged, except for the DASI score, which appeared to deteriorate in the
57
58 319 exercise group and increase in the usual care group, resulting in an overall difference in score
59
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3 320 of 4.93 (95% CI -0.94 to 10.80) and the mental component summary score of the SF12 which
4
5 321 improved in the usual care group, resulting in an overall difference in score of 4 (95% CI -3
6
7 322 to 10). Exercisers appeared to have a greater perception of the benefits of exercise compared
8
9 323 with those in the control group (3, 95% CI -4 to 11) (supplementary material 9).
10
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13 324

16 325 *Serious adverse events*

17
18 326 In total, n=13 (25%) experienced an SAE during the feasibility study, n=8 (33%) in the
19
20 327 exercise group and n=5 (19%) in the usual care group. The most common reasons for SAEs
21
22 328 were vascular access complications (n=3, 17%), stroke (n=3, 17%), acute coronary syndrome
23
24 329 (n=2, 11%) and non-specific chest pain (n=2, 11%). All events were classed as serious as
25
26 330 they resulted in hospitalisation. All events resolved, and none were directly related to the
27
28 331 intervention or trial.
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33 332

36 333 **Qualitative findings**

37
38 334 Thirty-seven patients were approached for the qualitative study. Twenty-six were recruited
39
40 335 and one died prior to data collection. Thirteen had participated in the feasibility trial. Nine
41
42 336 received dialysis during shifts randomised to exercise, and four randomised to usual care.
43
44 337 Twelve participants had declined to take part in the feasibility trial. Full characteristics for the
45
46 338 qualitative sample are provided in supplementary material 10.
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52
53 340 In addition to categories relating to the feasibility outcomes, categories relating to both the
54
55 341 delivery and the characteristics of a tailored exercise intervention were identified. These are
56
57 342 presented alongside illustrative quotes within Tables 3, 4, 5 and 6 and Figure 2.
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56 344 *Feasibility and acceptability of a definitive trial*
78 345 *Eligibility and recruitment*
9

10 346 Declining to participate was underpinned by a perception that the trial could worsen overall
11
12 347 health, particularly amongst those who had not previously participated in research or had
13
14 348 recently commenced HD. Female participants believed that exercise was predominantly for
15
16 349 men and that they were already doing enough daily activity, whilst participants living with
17
18 350 moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by
19
20 351 exercise. Motivators included a sense of altruism, and the perception that participation could
21
22 352 provide opportunities to improve individual outcomes; learn about their own health; and
23
24 353 access better healthcare. Participants felt that recruitment could be enhanced by the effective
25
26 354 use of non-verbal communication, rapport building, adaptation to study documentation and
27
28 355 actively involving family members in the recruitment process, as family support was often a
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33
34 356 prerequisite to participation (Table 3).

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37 357
3839 358 *Trial retention*
40

41
42 359 The primary reasons for withdrawal were becoming unwell, the duration of the trial and the
43
44 360 research not meeting participants expectations. Participants suggested that having a rapport
45
46 361 and maintaining regular dialogue with the research team might help retain participants within
47
48
49 362 a future trial (Table 3).
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363 *Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative*
364 *quotes.*

For peer review only

1
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3 365 *The acceptability of IDC*
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5 366 IDC was generally perceived to be a safe and positive use of HD treatment time. However,
6
7 367 IDC was described as limited in scope, and participants were uncertain of its impact,
8
9
10 368 particularly upon mobility, symptoms and falls (Table 4).
11
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13 369

16 370 *Table 4. Categories relating to the acceptability of IDC outcome acceptability and*
17 371 *illustrative quotes.*
18

19 372

22 373 *Outcome acceptability*
23

24 374 As indicated by participant quotations in Table 5, the number of outcomes and follow-ups
25
26 375 needed to be reduced and participants had a strong preference for outcomes that could be
27
28 376 collected during HD treatment. Many found the ISWT and STS60 assessments too
29
30 377 challenging. Participants were occasionally uncertain of the purpose of the questionnaires and
31
32 378 many reported difficulty quantifying symptom severity or a desire to provide ‘anticipated’
33
34 379 responses.
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42 381 Maintaining mobility, and the ability to undertake a range of ADLS and social roles were
43
44 382 viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative
45
46 383 study agreed to complete a falls diary and many reported they preferred falls information to
47
48 384 be collected during HD treatment. The majority who had fallen rarely reported them to
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50 385 healthcare professionals, believing that they were an expected consequence of HD or having
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52 386 had experience of their concerns about falls being overlooked. Consequently, falls prevention
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54 387 was not viewed as a key outcome.
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388 *Table 5. Categories relating to outcome acceptability and illustrative quotes.*

For peer review only

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3 389 *Perceptions of a tailored exercise programme*
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6 390 *Delivery*
7

8 391 There was no universally acceptable setting for exercise delivery (Table 6). Vulnerable and
9
10 392 mildly frail participants (CFS 4-5) were particularly open to group-based exercise in the
11
12 393 community or gym, which they felt would provide motivation through camaraderie with
13
14 394 others. However, access barriers due to HD treatment, complex health needs, and lack of
15
16 395 transport were common. Participants also described feeling self-conscious exercising
17
18 396 amongst 'normal' people. Home-based exercise was preferred by those with moderate to
19
20 397 severe frailty (CFS 6-7) due to easier access, greater flexibility and relevance to their daily
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22 398 activities. Despite this, concerns about lack of space and safety were highlighted by those
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24 399 who lived alone, whilst those with family were concerned about overburdening or injuring
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26 400 them by asking for support.
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3 401 *Table 6. Participants perceptions of the facilitators and barriers to group and home-based exercise.*
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For peer review only

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3 402 *Characteristics of a tailored exercise programme*
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5 403 Irrespective of the setting for delivery, participants identified several key features of a
6
7 404 tailored exercise intervention which are summarised in Figure 2.
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13 406 [FIGURE TWO. THE CORE COMPONENTS OF AN ACCEPTABLE EXERCISE
14
15 407 PROGRAMME FOR PEOPLE LIVING WITH FRAILITY AND RECEIVING
16
17 408 HAEMODIALYSIS TO BE INSERTED HERE]
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21 409

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23
24 410 *Preparation*

25
26 411 Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and
27
28 412 dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts
29
30 413 of exercise (for example breathlessness whilst exercising) were interpreted as worsening
31
32 414 symptoms or damage, and many participants were uncertain if exercise would be suitable or
33
34 415 beneficial. They indicated that the reason for exercising needed to be sufficiently compelling.
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36 416 They wanted to know what to expect prior to exercising, and individualised goal setting was
37
38 417 advocated to build motivation and appreciate improvements.
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46 419 *Content*

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48 420 Key components described were whole body resistance, aerobic and balance training. Many
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50 421 participants described being unable to get up once they had fallen and felt that practising this
51
52 422 was also important. Routine physical activity was viewed as more purposeful than structured
53
54 423 exercise 'for the sake of it' and participants spoke of their enjoyment of being outside and
55
56 424 engaging in meaningful and physically active hobbies.
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56 426 *Structure*
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8 427 Supervision was viewed as essential to select, teach and progress exercises. Individual
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10 428 tailoring which considered the impact of disability, comorbidities and fluctuating symptoms
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12
13 429 was important, and a choice of exercises, for example swimming, dancing and yoga, was
14
15 430 associated with increased enjoyment and engagement. Moderate to severely frail participants
16
17 431 wanted the programme to be progressed in a supportive and collaborative manner. Those who
18
19 432 were vulnerable or mildly frail wanted to be ‘pushed’ and progressed in a more assertive
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21 433 manner.
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28 435 Having a companion (typically peers, family or friends) was viewed as helping to overcome
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30 436 access barriers and provide socialisation and mutual motivation. The sharing of experience
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32 437 was also seen as a powerful means of challenging preconceptions about exercise ability,
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34 438 although participants with moderate to severe frailty raised concerns about feeling
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36 439 embarrassed or ‘judged’ if they were less able.
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43 441 **Integrated mixed-methods analyses**
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46 442 The integrated qualitative and quantitative findings suggest that an RCT of IDC is feasible for
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48 443 frail HD patients following adaptation. However, IDC should not be the only intervention
49
50 444 offered and the development of a multicomponent programme is warranted (Supplementary
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52 445 material 11).
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59 447 **DISCUSSION**
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3 448 These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to
4
5 449 increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was
6
7 450 viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest
8
9 451 that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity,
10
11 452 endurance and functional muscle strength and increase PA behaviour (steps/day). Despite
12
13 453 this, participants described a preference for a multi-component programme that prepared
14
15 454 them for exercise, offered variety, companionship and individualised supervision. No single
16
17 455 preferred environment for the delivery of this intervention was identified, but appeared to be
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19 456 influenced by frailty grade and individual factors.
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27 458 27% to 89% of secondary outcome measure data were missing, and, overall, this progression
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29 459 criterion was not achieved. Given that secondary measures are often insufficiently powered,
30
31 460 reducing the number collected within a future trial may improve completion.²⁶ Falls were not
32
33 461 of primary importance to participants, and aligns with the SONG-HD data which did not
34
35 462 identify falls as a key outcome.²⁷ Our findings suggest that accurately capturing prospective
36
37 463 falls data may be challenging due to under-reporting, and yet, retrospective falls data
38
39 464 collection does not fully reflect the incidence and impact of falls, particularly those which do
40
41 465 not require an ED visit or hospital admission. Given the high incidence of falls in this
42
43 466 population, capturing falls data may be important in a future trial, and regular prospective
44
45 467 recording of information relating to falls as a part of routine practice at the dialysis unit is
46
47 468 recommended, in line with participant feedback.⁵ This would provide both clinicians and
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49 469 researchers with higher quality data for use in both prospective and retrospective studies, and
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51 470 to inform clinical care.
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3 472 Further exploration and validation of meaningful measures for HD patients living with frailty
4
5 473 is also warranted. Some of the functional measures (the STS60 and ISWT) included were too
6
7 474 challenging. In the absence of a core set of functional outcome measures for older people, or
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10 475 people receiving haemodialysis, we suggest that the SPPB may be most appropriate and
11
12 476 feasible method of capturing information about mobility and function. Although challenges
13
14 477 with ceiling effects have been identified, this measure had the lowest levels of non-
15
16 478 completion within this study, and has demonstrated good test-retest reliability in HD patients
17
18 479 and excellent validity and responsiveness to change following an intervention in older adults.
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20
21 480 ^{28,29}To date, more comprehensive measures of basic and instrumental ADL ability and
22
23 481 participation have rarely been used in exercise studies. These outcomes were, however,
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25 482 highlighted as important within this study, and have also been included in guidelines and core
26
27 483 outcomes sets for HD and older people, warranting their inclusion in future exercise studies
28
29 484 relating to frail HD populations.^{27,30,31}
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36 486 The results of this study indicate that changes to eligibility criteria and screening are required.
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38 487 As only patient participants were interviewed, it was not possible to gain any insight on this
39
40 488 aspect of feasibility from the qualitative component. Importantly, the challenges of
41
42 489 identifying eligible participants do not appear to be unique to this study. Studies of older
43
44 490 people living with frailty highlight that large numbers need to be screened to achieve a 50%
45
46 491 recruitment rate, and a multicentre trial may be required.²⁶ Higher proportions older, female
47
48 492 and more severely frail HD patients declined to participate whilst the qualitative data indicated
49
50 493 this was due to negative perceptions relating to participation in both exercise and research.
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52 494 Such findings clearly have implications for the external validity of a future trial and the reach
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54 495 of the intervention at the point of implementation.²⁴
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6 497 To address this, this study suggests the recruitment strategies which utilise effective non-
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8 498 verbal communication skills to build rapport and explore participants' perceptions of the
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10 499 intervention and the research process, and subsequently provide balanced information about
11
12 500 the study, may lead to more representative recruitment. A sense of equipoise may be
13
14 501 preserved by emphasising altruism, access to potentially enhanced care, and an opportunity to
15
16 502 learn about their health (which were all identified as motivators to participation), rather than
17
18 503 the potential individual benefits of the intervention itself. Involving families and/or peer
19
20 504 supporters who have experience of the study and intervention in the recruitment process, and
21
22 505 introducing opportunities for participants to observe the exercise intervention, may also be
23
24 506 beneficial. Ultimately the selection of these strategies will depend upon the resources
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26 507 available and the need to strike a balance between conducting a trial with high internal and
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28 508 external validity and going beyond what is pragmatically possible to engage patients in the
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30 509 intervention at the implementation phase.
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511 This study suggests that IDC may reduce the incidence of falls resulting in ED visits and
512 hospital admissions in frail HD patients potentially by attenuating a decline in exercise
513 capacity, physical activity behaviour and function at levels shown to be clinically meaningful
514 in other long-term conditions.^{32,33} This indicates that preventing deterioration may be as
515 valuable, and more attainable, as improving outcomes in a frail population. Despite this, frail
516 participants experienced difficulties achieving the proposed level of exercise and maintaining
517 motivation in the face of varying symptomology. Exercise programmes have a dose-response,
518 and these factors may have reduced participants physical capability to exercise and achieve
519 optimal benefit, despite the overall good level of adherence. Clinical decision support tools

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3 520 have been used in other populations to rationalise exercise prescription, progression and
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5 521 amendment in the presence of varying symptomology, and a similar approach may be
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8 522 beneficial for frail HD patients.³⁴
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13 524 This study indicates that participants desire a multicomponent exercise programme, and
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16 525 require an intervention that addresses their particularly low levels of PA. Whilst step count
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18 526 and time spent in light and moderate PA increased following IDC, these were below PA
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20 527 recommendations for older people.³⁵ To date, PA interventions for HD patients have
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22
23 528 predominantly centred around walking, which may not be appropriate for those living with
24
25 529 frailty.³⁶⁻³⁹ This study suggests that functional training (task-orientated exercise which
26
27 530 engages multiple muscle groups) and physical activity that focuses on ‘doing more’ of these
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30 531 usual tasks may be more acceptable and efficacious. To date, two studies have employed
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32 532 similar approaches with non-frail HD patients. One study demonstrated significant
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34 533 improvements in lower extremity performance and the other a non-significant improvement
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36 534 in physical function and maintenance of other SF-36 domains compared with the control
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39 535 group.^{40,41} In older people without CKD who are living with frailty, functional training
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41 536 included as part of a multicomponent exercise programme is beneficial across a range of
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43 537 outcomes, including greater ability to rise from the floor following a fall.^{39,42-45} A similar
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45 538 approach to exercise prescription may be warranted in a frail HD population.
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51 540 Numerous barriers and facilitators to exercise were identified within this study, which have
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53 541 implications for the design of a programme. The use of theory is crucial in the development
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55 542 of effective interventions and the behaviour change wheel (BCW) is most frequently cited in
56
57 543 the development of interventions in CKD⁴⁶. Mapping the identified barriers and facilitators to
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3 544 the BCW indicates that ameliorating symptom burden prior to exercise, individualised
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5 545 exercise counselling, and a collaborative, problem-solving approach to exercise education are
6
7 546 most likely to encourage and sustain participation.^{46,47} Devising ways in which peer and
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10 547 family involvement can be incorporated into the programme may also increase motivation
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12 548 and opportunity to exercise but should be carefully managed given the potential for negative
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14 549 comparison amongst the frailest patients.

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20 551 A lack of preferred environment for intervention delivery may have implications for a
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22 552 definitive RCT. Exercise interventions require motivation, and limited engagement may
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24 553 negatively influence a trials external and internal validity. Ignoring patient preference is also
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26 554 out of step with clinical practice, where rehabilitation involves shared decision-making.
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29 555 Taken together, these factors have implications for determining treatment effects and future
30
31 556 intervention implementation.⁴⁸ There is increasing recognition that novel trial designs may be
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33 557 indicated when evaluating complex interventions and a Partially Randomised Patient
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35 558 Preference Trial, where participants without preference are randomised whilst those with a
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37 559 preference receive their choice, would provide information on both the efficacy of the
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39 560 intervention and the influence of preference.^{48,49}

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45 46 47 562 **Strengths and limitations**

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50 563 To our knowledge, this study is the first to examine the feasibility of an RCT of IDC for frail
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52 564 HD patients and to explore how trial procedures and exercise programmes should be
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54 565 specifically tailored to the needs of this group, from their own perspectives. Key strengths
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56 566 were the use of a validated frailty risk-stratification measure and multiple qualitative methods
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58 567 which provided a form of triangulation.⁵⁰ There were, however, challenges to recruiting

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3 568 severely frail participants, and those from a more diverse range of black and minority ethnic
4
5 569 groups, to both the trial and the qualitative study. Additionally, the views of clinicians and
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8 570 researchers were not explored. A future RCT should also blind outcome assessors to group
9
10 571 allocation to reduce the potential for detection bias. Finally, this study is exploratory and
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12 572 therefore all secondary measures of exercise capacity, function and PROMS should be
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14 573 interpreted with caution, not least due to the high number of participants who did not
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17 574 complete the follow up tests.
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23 576 **Conclusion**

26 577 In summary, this study suggests that a future definitive trial of IDC is feasible within a HD
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28 578 population with a CFS of 4-7 and paying particular attention in the design to those factors
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30 579 mentioned above may facilitate improved rates of eligibility and outcome completion.
31
32 580 Outcomes focusing on independence and participation should be the primary outcomes of
33
34 581 interest in a future trial. Whilst an exploratory analysis suggests some potential benefits to
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36 582 IDC, a tailored intervention comprising a comprehensive multi-component programme,
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38 583 symptom management, education and behaviour change is better suited to frail HD patients'
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40 584 needs.
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40

41 606 recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC,
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43

44 607 MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical
45

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47
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50

51 610 intellectual content during manuscript drafting or revision and accepts accountability for the
52

53 611 overall work by ensuring that questions pertaining to the accuracy or integrity of any portion
54

55 612 of the work are appropriately investigated and resolved. All authors have read and approved
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58 613 the final version
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6 615 **ETHICAL APPROVAL**
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9 616 This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and
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11 617 South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial
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14 618 and the qualitative component respectively
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20 620 **DATA SHARING STATEMENT**
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23 621 The datasets used and analysed during the current study are available from the corresponding
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25 622 author on reasonable request.
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23 756 Legends to Figures

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26 757 Figure 1.CONSORT

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29 758 Figure 2. The core components of an acceptable exercise programme for people living with
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31 759 frailty and receiving haemodialysis.

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37 761 **SUPPLEMENTARY MATERIAL**

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40 762 Supplementary material 1. Inclusion and exclusion criteria for the CYCLE-HD trial

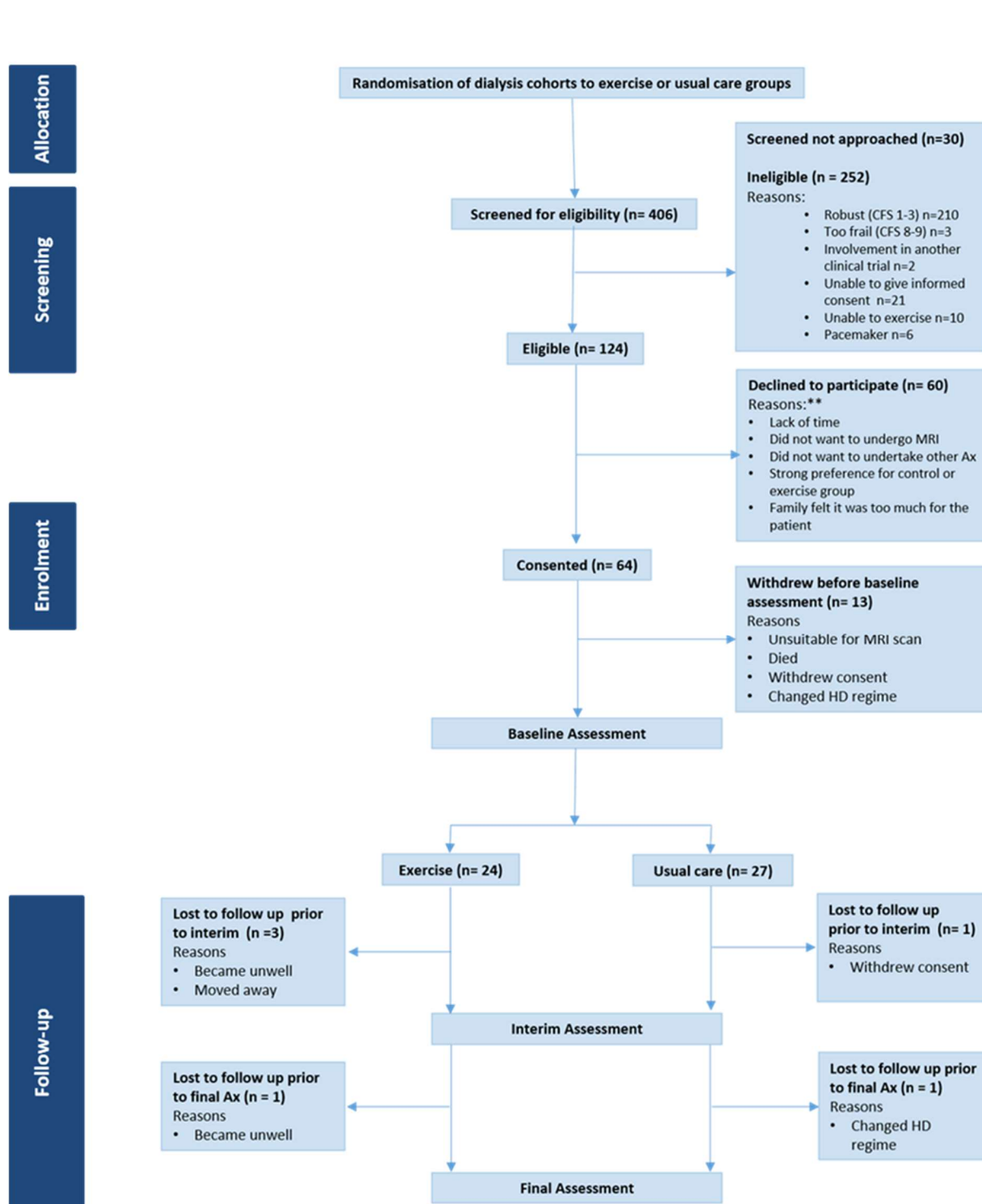
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43 763 Supplementary material 2. Summary of intervention characteristics, in line with TiDier
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45 764 guidance.

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48 765 Supplementary material 3. *A priori* progression criteria based on the primary feasibility
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50 766 objectives.

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53 767 Supplementary material 4. Patient-reported secondary outcome measures.

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56 768 Supplementary material 5. Interview topic guide questions.
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3 769 Supplementary material 6. Falls summary data and incidence of falls per person years.
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5 770 Supplementary material 7. Changes in exercise capacity and physical function after six
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7 771 months.
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10 772 Supplementary material 8. Changes in physical activity (accelerometry data) after six months.
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13 773 Supplementary material 9. Patient-reported outcomes measures after six months.
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16 774 Supplementary material 10. Baseline demographic and clinical characteristics for the
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18 775 qualitative participants.
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21 776 Supplementary material 11. Joint display of quantitative and qualitative results, with an
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23 777 overall assessment of mixed-methods inferences.
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Abbreviations: Ax, assessment; CFS, Clinical Frailty Scale; HD, haemodialysis.

Supplementary material 1. Inclusion and exclusion criteria for the *CYCLE-HD* trial.

Inclusion criteria	Exclusion criteria
Prevalent HD patient (> three months)	Unable to participate in current exercise programme due to perceived physical or psychological barriers
Aged 18 years or older	Unable to undergo MRI scanning (metal implants, severe claustrophobia)
Able and willing to give informed consent	Unfit to undertake exercise according to the American College of Sports Medicine (ACSM) guidelines

Supplementary material 2. Summary of intervention characteristics, in line with TiDier guidance.

Description of intervention.		A structured, supervised cycling exercise intervention delivered during in-centre HD.
Rationale.		<ul style="list-style-type: none"> Intradialytic cycling provides aerobic and low-level resistance training, is associated with increased adherence and is most widely used within practice.
What.	Materials provided to participants or used to support intervention delivery.	<ul style="list-style-type: none"> Cycling was delivered using the Moto Med Letto 2 (Medimotion Ltd). Materials: individualised exercise prescription and records of individual training bouts (duration (mins), intensity (RPE), resistance (gear), power output (watts) and energy expenditure (Kcal). General information on the benefits of exercise (posters and leaflets) available across all 3 HD centres.
	Materials used to train intervention providers.	Standardised progression and training protocol used by all providers.
Who (intervention providers).		<ul style="list-style-type: none"> Qualified exercise professionals with experience of delivering exercise to renal patients. All providers were directly involved in the study, and not delivering the sessions as part of a clinical role. Roles included exercise provision, supervision, monitoring and progression.
How (mode of delivery).		One to one, face to face.
Where (location).		Three HD units across the East Midlands, UK.
When and how much	The frequency of delivery.	Thrice weekly during each dialysis session.
	Target intensity of each bout of exercise.	RPE 12-14 (moderate intensity), cadence 60-70 RPM.
	Target duration of each bout of exercise.	At least 30 minutes of continuous exercise.
	The total duration of delivery.	Six months, with a one-month run-in period to achieve the target exercise prescription.
Tailoring.		<ul style="list-style-type: none"> The starting resistance (gear) based on the individual's tolerance. RPE used throughout to monitor and progress the exercise. Interval training was permitted.

Abbreviations: HD, haemodialysis; Kcal, kilocalories; RPE, rating of perceived exertion, RPM, revolutions per minute.

Supplementary material 3. A priori progression criteria based on the primary feasibility objectives.

Eligibility	Stop	Less than 20% of all patients eligible
	Go	More than 50% of all patients eligible
Recruitment	Stop	Less than 25% of eligible patients recruited
	Go	More than 50% of eligible patients recruited
Exercise acceptability	Stop	Less than 30% adherence to the exercise sessions
	Go	More than 70% adherence to the exercise sessions
Outcome acceptability	Stop	Less than 70% outcome measure completion
	Go	More than 80% outcome measure completion
Loss to follow-up	Stop	More than 40% loss to follow-up
	Go	Less than 20% loss to follow-up

Supplementary material 4. Patient-reported secondary outcome measures.

Patient-reported secondary outcome	Construct measured
12-item Short-Form Health Survey Version 2 (SF-12)	Generic health-related quality of life. Higher scores reflect better HRQoL. Scores are presented as a mental and physical component summary score.
Palliative care Outcomes Scale – Renal version (POS-R)	Renal specific measure of symptomology and symptom burden. A global symptom score was calculated by totalling all the scored items within the questionnaire. The mean number of symptoms, symptom severity was also calculated. Higher scores reflect greater symptom burden.
Hospital Anxiety and Depression Scale (HADS)	Emotional distress. A score of ≥ 14 indicates the presence of emotional distress in HD patients
The Exercise Self-Efficacy Scale (ESES)	Exercise confidence. Higher scores reflecting greater self-efficacy.
Dialysis Patient-Perceived Exercise Benefits and Barriers Scale (DPPEBBS)	HD patients' perceptions of benefits and barriers to exercise. Higher scores indicate a greater perception of the benefits of exercise over barriers.
The Dukes Activity Status Index (DASI)	Self-reported physical function. Higher scores indicate higher levels of physical function. The questionnaire was also used to estimate VO_2 peak.

HD, haemodialysis; HRQoL, Health-related quality of life.

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3 *Supplementary material 5. Interview topic guide question.*
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5 Diary
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- 9 1. Can you tell me about how you have been using the diary?
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11 2. If we asked patients to keep diaries like yours as part of a future study, what might help
12 them?
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14 3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell
15 me more about...?
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19 Exercise intervention for frailty and falls
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23 4. For some people exercising helps to prevent falls, make people more able and feel better.
24 How do you feel about exercising?
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26 5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have
27 you seen these bikes?
28
29 6. Programmes that are available for other people who fall include things like group exercise
30 and education. What do you think about this?
31
32 7. These programmes usually take place at the hospital. What do you think about this?
33
34 8. Some people prefer to do their exercise at home. What do you think about this?
35
36 9. Where do you think a programme should be run?
37
38 10. How often do you think you would be able to exercise?
39
40 11. Would you want any support to help you exercise?
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42 12. What might put you off exercising?
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44 13. What questions might you have before you decide to take part or not?
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46 14. If you did take part in some kind of exercise programme, what improvements would you
47 most like to see?
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51 Research
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- 53 15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE
54 study (declined/ took part. If took part completed/dropped out) if patient unsure]
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56 16. What do you think about the information you receive when deciding to take part in a
57 research study?
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3 17. Often researchers ask you to complete some assessments or tests to see if the thing they
4 are studying is effective or not. What do you think would help patients to complete these
5 assessments/ tests?
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8 18. Sometimes people don't complete the research study, which may happen for several
9 reasons [give examples as needed]. What do you think would help keep dialysis from
10 dropping out of research studies?
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12 19. What would you like to happen once you reach the end of the study?
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For peer review only

Supplementary material 6. Falls summary data and incidence of falls per person years.

	Usual care (n=27)	Exercise (n=24)
Number of Falls	11	5
Number (% of group) of non-fallers	19 (70)	20 (83)
Number (% of group) fallers (≥ 1 fall)	8 (30)	4 (17)
Number (% of group) frequent fallers (≥ 2 falls)	3 (11)	1 (4)
Person years	40.5	36
Incidence rate	0.27	0.14

For peer review only

Supplementary material 7. Changes in exercise capacity and physical function after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
ISWT (m)		n	16	15	36 (-12 to 84)
		Baseline	184 ± 130	237 ± 173	
		Final	158 ± 154	248 ± 192	
		Change	-26 ± 68	11 ± 63	
ESWT (secs)		n	14	15	181 (-92 to 453)
		Baseline	347 ± 384	401 ± 375	
		Final	193 ± 304	428 ± 423	
		Change	-153 ± 286	27 ± 413	
STS60 (n)		n	17	15	0 (-5 to 4)
		Baseline	10 ± 12	13 ± 11	
		Final	10 ± 13	13 ± 12	
		Change	0 ± 7	0 ± 6	
SPPB	Total score	n	17	15	0.5 (-0.7 to 2)
		Baseline	7 ± 3	9 ± 3	
		Final	6 ± 2	8 ± 3	
		Change	-1 ± 2	-0.5 ± 1	
	4m walk time (secs)	n	17	15	1 (-1 to 4)
		Baseline	7 ± 6	4 ± 1	
		Final	6 ± 4	5 ± 2	
		Change	1 ± 5	0 ± 1	
	Gait speed (m/s)	n	17	15	0.05 (-0.12 to 0.22)
		Baseline	0.74 ± 0.29	0.96 ± 0.28	
		Final	0.74 ± 0.28	0.91 ± 0.31	
		Change	0.00 ± 0.22	-0.05 ± 0.24	
	STS5 (secs)	n	9	10	5 (-4 to 15)
		Baseline	17 ± 7	16 ± 14	
		Final	23 ± 13	16 ± 10	
		Change	6 ± 11	0 ± 8	

Abbreviations: CI, confidence interval; ESWT, Endurance Shuttle Walk Test; ISWT, Incremental Shuttle Walk Test; m/s, metres per second; Secs, seconds; SPPB, Short Physical Performance Battery; STS5, Sit to Stand Five Repetitions; STS60, Sit to Stand in Sixty Seconds.

Supplementary material 8. Changes in physical activity (accelerometry data) after six months.

	Type of day		Usual Care	Exercise	Difference (95% CI)
Waking wear time (mins)	HD	n	5	10	244 (16 to 473)
		Baseline	891 ± 202	818 ± 183	
		Final	749 ± 105	921 ± 171	
		Change	-142 ± 166	103 ± 204	
	Non-HD	n	5	10	170 (-13 to 353)
		Baseline	893 ± 90	927 ± 216	
		Final	817 ± 134	1022 ± 165	
		Change	-75 ± 201	95 ± 129	
Steps (steps/day)	HD	n	5	10	859 (-825 to 2543)
		Baseline	2252 ± 4210	1373 ± 1080	
		Final	2464 ± 4783	2444 ± 1904	
		Change	211 ± 593	1070 ± 1665	
	Non-HD	n	5	10	888 (-84 to 1861)
		Baseline	3076 ± 5790	2387 ± 1696	
		Final	2645 ± 5284	2845 ± 2117	
		Change	-430 ± 603	458 ± 903	
Sedentary (mins/day)	HD	n	5	10	28 (-284 to 340)
		Baseline	954 ± 338	954 ± 203	
		Final	965 ± 208	992 ± 182	
		Change	10 ± 200	38 ± 287	
	Non-HD	n	5	10	124 (-205 to 454)
		Baseline	1022 ± 357	1103 ± 253	
		Final	912 ± 224	1117 ± 174	
		Change	-110 ± 298	14 ± 269	
Light PA (mins/day)	HD	n	5	10	91 (23 to -158)
		Baseline	125 ± 51	83 ± 42	
		Final	79 ± 39	127 ± 73	
		Change	-46 ± 45	44 ± 62	
	Non-HD	n	5	10	9 (-71 to 91)
		Baseline	145 ± 59	133 ± 50	
		Final	154 ± 99	151 ± 59	
		Change	9 ± 108	18 ± 44	
Moderate PA (mins/day)	HD	n	5	10	13 (-32 to 57)
		Baseline	83 ± 105	29 ± 33	
		Final	85 ± 123	43 ± 55	
		Change	1 ± 52	14 ± 29	
	Non-HD	n	5	10	20 (40 to -79)
		Baseline	79 ± 96	46 ± 61	
		Final	75 ± 112	62 ± 105	
		Change	-4 ± 40	16 ± 55	
Vigorous PA (mins/day)	HD	n	5	10	3 (-1 to 8)
		Baseline	4 ± 9	1 ± 1	
		Final	1 ± 2	1 ± 3	
		Change	-3 ± 7	0 ± 2	
	Non-HD	n	5	10	1 (0 to 2)
		Baseline	3 ± 0	1 ± 4	
		Final	2 ± 5	1 ± 4	
		Change	-1 ± 2	0 ± 0	

Abbreviations: CI, confidence interval; HD, haemodialysis; mins, minutes; PA, physical activity.

Supplementary material 9. Patient-reported outcomes measures after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
SF-12	PCS	n	19	19	0 (-4 to 5)
		Baseline	35 ± 9	35 ± 10	
		Final	36 ± 10	36 ± 10	
		Change	1 ± 7	1 ± 7	
	MCS	n	19	19	4 (-3 to 10)
		Baseline	43 ± 15	45 ± 13	
		Final	46 ± 13	45 ± 13	
		Change	4 ± 7	0 ± 12	
HADS	n	20	17	0 (-3 to 4)	
	Baseline	16 ± 10	15 ± 9		
	Final	14 ± 10	13 ± 9		
	Change	-2 ± 5	-2 ± 6		
POS-R	Global severity score	n	20	18	2 (-3 to 7)
		Baseline	19 ± 14	19 ± 14	
		Final	18 ± 14	20 ± 14	
		Change	1 ± 6	-1 ± 9	
	mean severity	n	20	18	0 (0 to 0)
		Baseline	2 ± 1	2 ± 1	
		Final	2 ± 1	2 ± 1	
		Change	0 ± 0	0 ± 0	
	mean number	n	22	16	0 (-1 to 2)
		Baseline	9 ± 4	10 ± 4	
		Final	9 ± 4	10 ± 5	
		Change	0 ± 4	0 ± 2	
ESES	n	19	16	0 (-1 to 1)	
	Baseline	2 ± 2	2 ± 1		
	Final	2 ± 1	2 ± 1		
	Change	0 ± 1	0 ± 1		
DPPEBBS	n	19	15	3 (-4 to 11)	
	Baseline	59 ± 10	59 ± 15		
	Final	61 ± 10	65 ± 7		
	Change	2 ± 7	6 ± 14		
DASI	n	20	18	4.93 (-0.94 to 10.80)	
	Baseline	13.06 ± 12.85	20.29 ± 14.33		
	Final	17.29 ± 14.41	19.60 ± 14.59		
	Change	4.22 ± 9.72	-0.71 ± 7.92		

Abbreviations: CI, confidence interval; DASI, Duke Activity Status Index; DPPEBBS, Dialysis Patients Benefits and Barriers Scale; ESES, Exercise Self efficacy Scale; HADS, Hospital Anxiety and Depression Scale; MCS, mental component summary score; POS-R, Palliative Outcomes Scale Renal, PCS, physical component summary score; VAS, visual analogue scale.

Supplementary material 10. Baseline demographic and clinical characteristics for the qualitative participants.

	N=25	
Age (years)	69±10	
Gender n (%)	Female	13 (52%)
	Male	12 (48%)
Ethnicity n (%)	White background	13 (52%)
	Asian or Asian British	10 (40%)
	Caribbean	1 (4%)
	Not stated	1 (4%)
Diagnosis	Diabetic nephropathy	11 (44%)
	Aetiology uncertain	6 (24%)
	Chronic pyelonephritis	3 (12%)
	Atypical hemolytic uremic syndrome	1 (4%)
	FSGS	1 (4%)
	Henoch-Schönlein Purpura	1 (4%)
	Minimal change nephropathy	1 (4%)
	Polycystic kidney disease	1 (4%)
CCI	6±2	
Time on HD (months)	43 (IQR 16-85)	
CFS n (%)	Vulnerable	9 (36%)
	Mildly frail	5 (20%)
	Moderately frail	8 (32%)
	Severely frail	3 (12%)
Number of falls in the last six months	3 (IQR 2-4)	
Previous transplant n (%)	No	21 (84%)
	Yes	4 (16%)
Active on transplant list n (%)	No	22 (88%)
	Yes	3 (12%)

Abbreviations: CCI, Charlson comorbidity index; CFS, clinical frailty scale; FSGS, Focal segmental glomerulosclerosis; HD, haemodialysis.

Supplementary material 11. Joint display of quantitative and qualitative results, with an overall assessment of mixed-methods inferences.

	Progression criteria	Feasibility trial	Qualitative results	Mixed-methods inferences
Eligibility	STOP <20% GO >50% eligible.	31% patients eligible	No discussion. Patients not involved in screening process	Silence
Recruitment	STOP <25% GO >50% recruited.	52% eligible patients recruited.	<ul style="list-style-type: none"> - Frailer and female participants less likely to be approached despite eligibility and have more concerns about the suitability - Perception that risks outweigh the potential benefit - Recruitment processes could be improved 	Complementary
Retention	STOP >40% GO <20% lost to follow-up.	12 % loss to follow-up. Reasons predominantly unavoidable (death, ill-health).	Loss to follow-up attributed to: <ul style="list-style-type: none"> - Illness; - length of trial; - the reality of being in the study not meeting expectations. 	Complementary
Intervention	STOP <30% GO >70% adherence over six-months.	74% adherence rate across the six-month exercise duration.	<ul style="list-style-type: none"> - IDC good use of time. - Participants felt safe and felt well supported. - IDC limited in scope. - Participants described a range of other important components 	Complementary
Outcome	STOP <70% GO >80% outcome measure completion.	Up to 89% of secondary outcome measure data missing Collection of falls data challenging.	<ul style="list-style-type: none"> - Number of outcomes measured to be reduced. - Outcome testing during HD or at home preferred. - 52% agreed to complete a falls diary, 12% lost. - STS60, ESWT and ISWT unsuitable - Researcher support and family involvement may increase completion - Outcomes measuring ADLs, participation and symptom prioritised 	Complementary Silence for PA monitoring.

Results from the feasibility trial are colour coded to depict whether they met the 'stop' (red), 'go' (green) or 'change' (orange) progression criteria.

Abbreviations: ADLs, activities of daily living; ESWT, Endurance Shuttle Walk Test; IDC, intradialytic exercise; ISWT, Incremental Shuttle Walk Test; PA, physical activity; STS60, sit to stand in sixty seconds.



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6
	2b	Specific objectives or research questions for pilot trial	6-7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7 and supplementary material 1
	4b	Settings and locations where the data were collected	7-8,10-11
	4c	How participants were identified and consented	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8 and supplementary material 2
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9-11, supplementary materials 3,4 and 5
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	9 and supplementary material 3
Sample size	7a	Rationale for numbers in the pilot trial	8-9

	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	12-13 figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	12-13 figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 (trial) supplementary material 10 (qualitative)
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Supplementary materials 6-9 and page 15-17
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplementary materials 6-9 and page 15-17
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	17- 26
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P 17
	19a	If relevant, other important unintended consequences	n/a
Discussion			

1	Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	30
2	Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	26-31
3	Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	26-31
4		22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	26-31
5	Other information			
6	Registration	23	Registration number for pilot trial and name of trial registry	4 and 7
7	Protocol	24	Where the pilot trial protocol can be accessed, if available	7
8	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31
9		26	Ethical approval or approval by research review committee, confirmed with reference number	32

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15 Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. 2016;355.

16 *We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important
17 clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological
18 treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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Exercise for people living with frailty and receiving haemodialysis: a mixed-methods randomised controlled feasibility study.

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	REHABILITATION MEDICINE, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

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4 1 **Exercise for people living with frailty and receiving haemodialysis: a mixed-**
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7 2 **methods randomised controlled feasibility study.**
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3 41 **ABSTRACT**
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6 42 **Objectives**
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9 43 Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This
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11 44 study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic
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13 45 exercise is feasible for frail HD patients, and explore how the intervention may be tailored to
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16 46 their needs.
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19 47 **Design**
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22 48 Mixed-methods feasibility.
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25 49 **Setting & participants**
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28 50 Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7
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30 51 (vulnerable to severely frail) were eligible for the feasibility study.
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33 52 **Interventions**
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36 53 Participants in the exercise group undertook six-months of thrice-weekly, progressive,
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38 54 moderate intensity intradialytic cycling (IDC).
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41 55 **Outcomes**
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44 56 Primary outcomes were related to feasibility. Secondary outcomes were falls incidence
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46 57 measured from baseline to one year following intervention completion, and exercise capacity,
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48 58 physical function, physical activity and patient-reported outcomes (PROMS) measured at
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50 59 baseline and six months. Acceptability of trial procedures and the intervention were explored
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52 60 via diaries and interviews with n=25 frail HD patients who both participated in (n=13, 52%),
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54 61 and declined (n=12, 48%), the trial.
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59 62 **Results**
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3 63 124 (31%) patients were eligible, and of these 64 (52%) consented with 51 (80%)
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5 64 subsequently completing a baseline assessment. N=24 (71% male; 59 ± 13 years) dialysed
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7 65 during shifts randomly assigned to exercise and n=27 (81% male; 65 ± 11 years) shifts
8
9 66 assigned to usual care. N=6 (12%) were lost to follow-up. The exercise group completed 74%
10
11 67 of sessions. 27 to 89% of secondary outcome data were missing. Frail HD patients outlined
12
13 68 several ways to enhance trial procedures. Maintaining ability to undertake activities of daily
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15 69 living and social participation were outcomes of primary importance. Participants desired a
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17 70 varied exercise programme.
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22 71 **Conclusions**

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25 72 A definitive RCT is feasible, however a comprehensive exercise programme may be more
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27 73 efficacious than IDC in this population.
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30 74 **Trial Registration**

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33 75 ISRCTN11299707; ISRCTN12840463
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39 77 **Keywords:** feasibility; frailty; exercise; haemodialysis; mixed-methods.
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78 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 79 • To our knowledge, this is the first study to evaluate the feasibility of an exercise
80 intervention for people living with frailty and receiving haemodialysis (HD).
- 81 • The Clinical Frailty Scale, a frailty risk-stratification measure which has been
82 validated in an HD population, was used to identify eligible participants.
- 83 • This study is also the first to explore how trial procedures and exercise programmes
84 should be specifically tailored to the needs of people living with frailty and receiving
85 HD, from their own perspectives.
- 86 • Multiple qualitative methods (interviews and diaries) were used to explore
87 participants perceptions, providing a form of triangulation which strengthens the
88 conclusions made.
- 89 • Due to the nature of the intervention and resource limitations, we could not blind
90 intervention providers, outcome assessors or study participants to group allocation.

91 INTRODUCTION

92 Frailty, “a multidimensional syndrome of decreased physiological reserve leading to
93 increased vulnerability to minor health stressors”, is highly prevalent within the
94 haemodialysis (HD) population.^{1,2} Increasing frailty is associated with worsening outcomes,
95 including mortality, hospitalisation, falls, reduced Health-Related Quality of Life (HRQoL),
96 psychological well-being, physical function, ability to undertake activities of daily living
97 (ADLs) and increased symptom burden.³⁻⁵

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99 Despite this, frailty is not static and evidence suggests that some factors associated with
100 frailty are amenable to change.⁶ Whilst the possible mediating role of exercise has been
101 discussed, to our knowledge no original studies have examined the feasibility or effectiveness
102 of an exercise programme for people living with frailty and receiving HD.⁷ To date, exercise
103 interventions for HD patients have focused upon intradialytic exercise, most commonly
104 delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about
105 whether this is the most appropriate training stimulus for frail HD patients.⁸ In addition, HD
106 treatment can be poorly tolerated by frail patients and therefore IDC may represent an
107 additional stressor to which these patients are particularly vulnerable.⁹ European renal best
108 practice guidance highlights a need for studies which identify how exercise programmes
109 should be more specifically tailored to the needs of frail CKD patients¹⁰, yet to date, there has
110 also been no exploration of the needs, barriers and facilitators to exercise from the
111 perspectives of people living with frailty and receiving HD themselves.

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113 The aim of this study was to determine the feasibility of conducting an RCT investigating the
114 effects of IDC for HD patients living with frailty by: (i) estimating rates of eligibility,

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3 115 recruitment, retention, exercise adherence and outcome acceptability; and exploring (ii) the
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5 116 potential benefits of IDC across a range of secondary outcomes; and (iii) the perceptions of
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7 117 frail HD patients in relation to participating in clinical research, IDC and a tailored exercise
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9 118 intervention.

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14 15 16 120 **METHODS**

17 18 19 121 **Design**

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22 122 A prospective, randomised controlled feasibility study was conducted alongside concurrent
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24 123 qualitative diaries and interviews (Trial Registration numbers ISRCTN11299707;
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26 124 ISRCTN12840463). The feasibility study was a secondary analysis of the *CYCLE-HD* trial,
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28 125 whose aims and methods are reported elsewhere.¹¹ The qualitative component was
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30 126 underpinned by a constructivist Grounded Theory approach.¹² All participants provided
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32 127 written informed consent.

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37 38 39 129 **Participants**

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42 130 Prevalent adult (over 18 years) HD patients were recruited from three centres within the UK
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44 131 East Midlands Renal Network. In addition to the inclusion and exclusion criteria for the
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46 132 *CYCLE-HD* trial (supplementary material 1), the Clinical Frailty Scale (CFS), a risk
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48 133 stratification tool, was used to identify vulnerable to severely frail participants (CFS score 4-
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50 134 7).¹³ The CFS has good predictive abilities in an HD population, good construct validity
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52 135 when compared with the Frailty Index, is less burdensome than the Frailty Phenotype, and has
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54 136 been validated in an HD population.¹³⁻¹⁵

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3 137 The inclusion and exclusion criteria for the qualitative component mirrored the feasibility
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5 138 study and both those involved in the trial, and those who were eligible but declined to
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7 139 participate, were eligible.
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12 13 14 141 **Randomisation**

15
16 142 HD cohorts were randomised prior to screening, based on a computer-generated
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18 143 randomisation algorithm held by the Robertson Centre for Biostatistics at the University of
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20 144 Glasgow.
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25 26 27 146 **Recruitment**

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30 147 Patients were screened for eligibility by their supervising nephrologist. Suitable patients were
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32 148 approached during HD, and the study explained. For the qualitative component, participants
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34 149 who had been involved in the feasibility study were recruited following completion of, or
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36 150 withdrawal from, the trial to prevent contamination.
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41 42 43 152 **Exercise intervention**

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46 153 Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance.¹⁶
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48 154 Briefly, following a one-month run-in, participants in the exercise group undertook thrice-
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50 155 weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC
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52 156 (MOTomed Letto2, Reck, Germany), for six months.¹⁷ Cycling resistance was progressively
53
54 157 increased to maintain RPE in response to exercise adaptation. Both arms continued with usual
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56 158 care HD as described elsewhere.¹¹
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56 160 **Sample size**
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9 161 Determinations of sample size from a power calculation around a primary outcome are not
10 162 relevant to a feasibility study and sample sizes of 24-50 are considered sufficient.¹⁸ For the
11 163 qualitative component maximum variation sampling was initially used to ensure diversity in
12 164 frailty status and level of trial participation.¹² As understanding was gained from preliminary
13 165 analyses, theoretical sampling was used to further recruit participants.¹² A maximum of 30
14 166 interviews were planned, but data collection ceased at the point where theoretical categories
15 167 were saturated and no longer generated new insight (n=25).

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2526 169 **Primary outcome measures**
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29 170 The primary feasibility outcomes are presented in supplementary material 3. Judgement
30 171 regarding feasibility was based upon a set of *a priori* progression criteria. For each criterion,
31 172 the development of ‘stop’ (indicating when there are issues with the trial that cannot be
32 173 resolved) and ‘go’ thresholds (when there are no issues that may impede the success of a
33 174 trial) were co-produced by patients, clinicians and researchers.^{19,20} Results falling between
34 175 these thresholds indicated that adaptation to trial procedures may render a definitive RCT
35 176 viable.²⁰

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5051 178 **Baseline demographic and clinical variables**
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54 179 Demographic and clinical characteristics were gathered from participants’ medical notes. The
55 180 Charlson Comorbidity Index (CCI) was used to estimate the burden of comorbid disease.²¹

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3 **182 Secondary outcome measures**
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6 183 Multiple secondary outcomes were used to determine the potential effects of IDC and most
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8 184 appropriate primary endpoint for a future RCT. Outcome assessors were not blinded to group
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10 allocation.
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16 187 Information on the number of falls, defined as ‘an unexpected event in which the participants
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18 188 come to rest on the ground, floor, or lower-level’ which resulted in Emergency Department
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20 189 visits and hospital admissions were collected from baseline to one year following intervention
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22 190 completion from medical records and hospital episode statistics.²²
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29 192 Field tests of exercise capacity and physical function included the Incremental Shuttle Walk
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31 193 Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance
32
33 194 Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60).¹¹ Physical activity (PA) was
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35 195 objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc.,
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37 196 Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were
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39 197 used to ensure representative data for average daily wear-time, steps per day, and time
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41 198 (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS)
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43 199 moderate (3-6 METS) and vigorous (>6 METS) PA.²³ PROMs collected are outlined in
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45 200 supplementary material 4.¹¹ All outcomes were collected at baseline and six months.
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54 202 Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as
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56 203 outlined previously.¹¹
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205 **Diaries and interviews**

206 Participants first completed a prospective falls diary, recognised as the current 'gold
207 standard' for falls data collection, for up to three months to examine the feasibility of this
208 outcome measure within a future definitive RCT.²² Semi-structured interviews then explored
209 participants' experiences of: (i) keeping a falls diary; (ii) participating in a trial; and (iii) their
210 perceptions of IDC and a tailored exercise intervention.

211
212 Information to support diary collection and a topic guide for the interviews (supplementary
213 material 5) was developed by HMLY, HE and a patient and public involvement group.
214 Topics were tailored according to the level of involvement in the trial, and the content of
215 diaries. Interviews were conducted during HD, in the participant's home, or in the hospital by
216 HMLY and lasted 20 to 120 minutes (mean 63 minutes). All were digitally audio-recorded
217 and transcribed verbatim.

219 **Data analysis**

220 Sample characteristics are presented as mean \pm standard deviation, median (IQR) or n (%), as
221 appropriate. Descriptive statistics and confidence intervals were used to estimate feasibility
222 outcomes.²⁴ The percentage of exercise sessions completed was used to establish the
223 acceptability of IDC. Outcome acceptability was determined by quantifying the amount of
224 missing data across secondary outcomes. No imputation was performed to account for
225 missing data. No statistical testing relating to the efficacy of the exercise intervention was
226 undertaken, although the potential benefits of exercise were estimated.²⁴ For falls, summary
227 data, incident rate ratio (the ratio of the incidence rate in the exercise group divided by the
228 incidence rate in the usual care group) and 95% confidence intervals were presented.

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3 229 Statistical analyses were performed using SPSS 24 (IBM UK Ltd, UK) and Stata 16
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5 230 (StataCorp LCC, USA).

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11 232 Qualitative analysis was undertaken by HMLY and SG and informed by a constant
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13 233 comparative approach.¹² Transcripts were reviewed, then coded line by line, followed by
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15 234 focused, and then theoretical, coding.¹² NVivo11 software (QSR International Ltd, version
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17 235 11, 2016) was used to facilitate data management. Finally, qualitative and quantitative results
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19 236 were merged in a 'joint display' to facilitate an overall assessment of feasibility.²⁵

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24 238 **Patient and public involvement**

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27 239 The patient and public involvement (PPI) group for this study comprised patients of all ages,
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29 240 genders and ethnicities who were living with frailty and receiving HD, and their relatives.
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31 241 They agreed this study was an important priority for further investigation and particularly
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33 242 stressed the need to add the qualitative component. The PPI group were involved early in the
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35 243 ethical approval stages and were actively engaged in writing lay summaries and providing
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37 244 patient perspectives on data collection procedures, ethical issues, and the study dissemination
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39 245 plans. They assisted in the preparation of study documentation, interview topic guides and
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41 246 diary keeping materials. During the study, members of the PPI group attended regular
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43 247 steering meetings and were involved in co-producing the progression criteria.
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52 249 **RESULTS**

53 250 **Feasibility study**

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3 251 *Eligibility and recruitment*
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5 252 Screening and recruitment took place from March 2015 to 2018, with data collection
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7 253 completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients
8
9 254 screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as
10
11 255 vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four
12
13 256 participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of
14
15 257 time or family support and reluctance to undergo outcome testing, or to be randomised. Those
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17 258 who declined to participate had a median age of 73 (IQR 67-81) years. N=35 (58%) were
18
19 259 female and n=27 (42%) male. Twenty-five (42%) were classified as vulnerable according to
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21 260 the CFS, n=17 (28%) were mildly frail, n=9 (15%) moderately frail and n=9 (15%) severely
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23 261 frail. Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline
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25 262 assessment. N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four
26
27 263 (47%) participants received dialysis during shifts randomised to exercise and twenty-seven
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29 264 (53%) during shifts randomised to usual care.
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36 265 [FIGURE ONE TRIAL CONSORT TO BE INSERTED HERE]
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42 267 *Participant characteristics*
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44 268 Table 1 displays the characteristics of the trial participants at baseline. Groups were well
45
46 269 matched across most variables. A lower proportion of participants were female (23.5%) and
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48 270 severely frail (6%) overall.
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271 *Table 1. Baseline demographic and clinical characteristics of the trial participants.*

		Usual care (n=27)	Exercise (n=24)	All (n=51)
Age (years)		65 ± 11	59 ± 13	63 ± 12
Sex (n, %)	Female	5 (18.5%)	7 (29%)	12 (23.5%)
Ethnicity (n, %)	White	12 (44%)	11 (46%)	23 (45%)
	Asian or Asian British	11 (41%)	11 (46%)	22 (43%)
	Caribbean	1 (4%)	0 (0%)	1 (2%)
	Other ethnic	1 (4%)	1 (4%)	2 (4%)
	Not stated	2 (7%)	1 (4%)	3 (6%)
Diagnosis (n, %)	Aetiology Uncertain	8 (29%)	7 (29%)	15 (29%)
	Diabetic Nephropathy	5 (19%)	7 (29%)	12 (23%)
	Glomerulonephritis	5 (19%)	3 (14%)	8 (16%)
	Renal Vascular Disease	3 (11%)	2 (8%)	5 (10%)
	Other diagnoses	4 (15%)	1 (4%)	5 (10%)
	Chronic Pyelonephritis	2 (7%)	1 (4%)	3 (6%)
	Polycystic Kidney Disease	0 (0%)	2 (8%)	2 (4%)
	Not recorded	0 (0%)	1 (4%)	1 (2%)
CCI		5 ± 2	5 ± 2	5 ± 2
Previous transplant (n, %)	No	21 (75%)	18 (75%)	39 (76.5%)
	Yes	6 (21%)	6 (25%)	12 (23.5%)
Time on HD (months)		17 (7-53)	13 (10-61)	16 (8-53)
BMI (kg/m ²)		27.38 ± 6.72	25.87 ± 5.28	26.67 ± 6.07
Total no. medications		12 ± 4	12 ± 4	12 ± 4
Clinical Information	Albumin (g/L)	35.4 ± 4.4	37.4 ± 4.3	36.4 ± 4.4
	Haemoglobin (g/L)	107 ± 12	112 ± 17	107 ± 15
Haemodialysis	URR (%)*	74 (70-80)	75 (58-79)	74 (71-79)
	SBP (mmHg)	143 ± 21	144 ± 21	144 ± 21
	DBP (mmHg)*	65 (62-78)	78 (69-86)	76 (62-81)
CFS (n, %)	4, Vulnerable	13 (48%)	10 (42%)	23 (45%)
	5, Mildly frail	5 (18.5%)	7 (29%)	12 (23.5%)
	6, Moderately frail	8 (30%)	5 (21%)	13 (25.5%)
	7, Severely frail	1 (3.5%)	2 (8%)	3 (6%)

272 *Values reported are mean and SD (±), except for *median and IQR. Abbreviations: BMI, body mass*
 273 *index; CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale DBP, diastolic blood pressure;*
 274 *SBP, systolic blood pressure; URR, urea reduction ratio.*

275 *Retention*

276 Six (12%, 95% CI 4.4% to 23.9%) participants were lost to follow-up: three participants
 277 withdrew due to ill-health, one moved away, one changed HD regime and one withdrew
 278 consent.

279

280 *Exercise adherence*

281 A mean of 61 ± 17 exercise sessions were completed over the six-month intervention,
 282 representing an adherence rate of $74 \pm 20\%$. The most frequent reasons for missing an exercise
 283 session were declining ($n = 175$ out of 535 sessions omitted in total, 33%), feeling unwell ($n =$
 284 116, 22%) and pain ($n = 105$, 20%). Table 2 summarises the mean amount of exercise
 285 achieved. On average, participants reached the prescribed level of exercise by six months,
 286 although $n = 18$ (75%) were unable to achieve this by the end of the one-month run-in period.

287 *Table 2 Mean (SD) exercise achieved per session over the six-month duration of the*
 288 *intervention.*

Duration (mins)	35 ± 8
Speed (RPM)	63 ± 10
Intensity (RPE)	13 ± 1
Gear	9 ± 4
Distance (Miles)	7 ± 3
Power (Watts)	13 ± 6
Energy expenditure (Kcals)	64 ± 31

289 *All data presented as mean and SD (\pm). Abbreviations: kcals, kilocalories, mins, minutes; RPE, rating*
 290 *of perceived exertion; RPM, revolutions per minute.*

291
 292 *Outcome acceptability*

293 For tests of exercise capacity (ISWT and ESWT); $n = 14$ (27%) did not complete at least one
 294 test at baseline, $n = 30$ (64%) at interim and $n = 26$ (58%) at final. For tests of physical function;
 295 $n = 20$ (39%) did not complete at least one test at baseline, $n = 33$ (70%) at interim and $n = 30$
 296 (67%) at final. For PROMs; $n = 27$ (53%) did not complete at least one questionnaire at

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3 297 baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were
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5 298 missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the
6
7 299 primary reason for non-completion for all outcomes across all time points.
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14 301 *Secondary outcomes*

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16 302 Summary falls data are presented in supplementary material 6. The crude falls incident rate
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18 303 ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased
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20 304 incidence of falls within the usual care group.
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26 306 Exercise capacity was maintained in the exercise group, but deteriorated in the usual care
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28 307 group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181
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30 308 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also
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32 309 increased in the usual care group (suggesting a deterioration in function), but was maintained
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34 310 in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15)
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36 311 (supplementary material 7).
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44 313 Step count increased in the exercise group resulting in an overall difference of 859 steps/day
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46 314 (95%CI -825 to 2543) on HD days and 888 steps/day (95%CI -84 to 1861) on non-HD days.

47
48 315 Whilst sedentary time was increased in the exercise group on all days compared with the
49
50 316 usual care group, this appeared to be offset by increases in light PA and moderate PA, and
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52 317 maintenance (albeit of low levels) of vigorous PA versus maintenance or deterioration across
53
54 318 the same metrics in the usual care group (supplementary material 8). For PROMs, outcomes
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56 319 were largely unchanged, except for the DASI score, which appeared to deteriorate in the
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58 320 exercise group and increase in the usual care group, resulting in an overall difference in score
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3 321 of 4.93 (95% CI -0.94 to 10.80) and the mental component summary score of the SF12 which
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5 322 improved in the usual care group, resulting in an overall difference in score of 4 (95% CI -3
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7 323 to 10). Exercisers appeared to have a greater perception of the benefits of exercise compared
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9 324 with those in the control group (3, 95% CI -4 to 11) (supplementary material 9).

10 325

16 326 *Serious adverse events*

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18 327 In total, n=13 (25%) experienced an SAE during the feasibility study, n=8 (33%) in the
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20 328 exercise group and n=5 (19%) in the usual care group. The most common reasons for SAEs
21
22 329 were vascular access complications (n=3, 17%), stroke (n=3, 17%), acute coronary syndrome
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24 330 (n=2, 11%) and non-specific chest pain (n=2, 11%). All events were classed as serious as
25
26 331 they resulted in hospitalisation. All resolved, and none were directly related to the
27
28 332 intervention or trial.

29 333

35 334 **Qualitative findings**

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38 335 Thirty-seven patients were approached for the qualitative study. Twenty-six were recruited
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40 336 and one died prior to data collection. Thirteen had participated in the feasibility trial. Nine
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42 337 received dialysis during shifts randomised to exercise, and four randomised to usual care.
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44 338 Twelve participants had declined to take part in the feasibility trial. Full characteristics for the
45
46 339 qualitative sample are provided in supplementary material 10.

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51 341 In addition to categories relating to the feasibility outcomes, categories relating to both the
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53 342 delivery and the characteristics of a tailored exercise intervention were identified. These are
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55 343 presented alongside illustrative quotes within Tables 3, 4, 5 and 6 and Figure 2.

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56 345 *Feasibility and acceptability of a definitive trial*
78 346 *Eligibility and recruitment*
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10 347 Declining to participate was underpinned by a perception that the trial could worsen overall
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12 348 health, particularly amongst those who had not previously participated in research or had
13
14 349 recently commenced HD. Female participants believed that exercise was predominantly for
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16 350 men and that they were already doing enough daily activity, whilst participants living with
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18 351 moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by
19
20 352 exercise. Motivators included a sense of altruism, and the perception that participation could
21
22 353 provide opportunities to improve individual outcomes; learn about their own health; and
23
24 354 access better healthcare. Participants felt that recruitment could be enhanced by the effective
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26 355 use of non-verbal communication, rapport building, adaptation to study documentation and
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28 356 actively involving family members in the recruitment process, as family support was often a
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30 357 prerequisite to participation (Table 3).
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40 359 *Trial retention*
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42 360 The primary reasons for withdrawal were becoming unwell, the duration of the trial and the
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44 361 research not meeting participants expectations. Participants suggested that having a rapport
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46 362 and maintaining regular dialogue with the research team might help retain participants within
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48 363 a future trial (Table 3).
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364 *Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative*
 365 *quotes.*

Eligibility and recruitment	
Challenges to recruitment	<ul style="list-style-type: none"> • [Interviewer]: "Have you ever taken part in any research before?" [Participant]: "No. I have not been asked really" (Female, moderately frail). • "If anything happens I am in trouble, I would rather avoid it [research]" (Male, severely frail). • "I don't think I had been dialysing all that long and I didn't know how [the trial] would affect me" (Male, mildly frail). • "I do enough, I am always out, up-down, do this, do that, I have just put clothes in the machine you know for a wash, I go for a shower you know" (Female, mildly frail). • "You have got to take age into consideration. Now I am getting old and there is a limit to what I can do. And it doesn't get any easier it gets worse" (Female, moderately frail)
Motivators to participation	<ul style="list-style-type: none"> • "If it helps someone else who has the same problem as me, they might be able to do something for him that they couldn't do for me" (Male, moderately frail). • "I found the [outcome measures] very beneficial actually...it kind of educated me at the time...educationally it was informative" (Male, vulnerable). • "What I like about research is that you are better looked after. I think if patients were a bit more aware that you are going to get preferential treatment, I think it would make it more attractive" (Female, vulnerable).
Suggested methods of enhancing recruitment	<ul style="list-style-type: none"> • "The research team should be there and explain that they don't want much, explain the benefits. Explain it's not for us [the research team] it's for the patients benefit, let them try and if then it doesn't go well [the participant] can stop it... it's not the information you give but talking as a person that's more important" (Male, vulnerable). • "If I have got confidence in [the researcher] and that [they] know what they are doing and why, then it's fine" (Male, mildly frail). • "I don't like it [the text] is too tiny, I can't even read [the information sheet] with reading glasses on...a picture or two might also help" (Female, mildly frail). • "There's a lot of sheets in [the information sheet], I think people will get fed up reading all that" (Female, mildly frail)
Trial retention	
	<ul style="list-style-type: none"> • "I have thought of dropping out because I am unable to do much. I am not interested because...I am not well. I have got a lot of things [wrong] with my body" (Female, mildly frail). • "Somebody recently asked me about research and I tried it for about three weeks and I said no, not for me...I thought no, this is not what I want, it's not particularly helpful" (Female, moderately frail).

366 *The acceptability of IDC*

367 IDC was generally perceived to be a safe and positive use of HD treatment time. However, it
 368 was also described as limited in scope, and participants were uncertain of its impact,
 369 particularly upon mobility, symptoms and falls (Table 4).

370

371 *Table 4. Categories relating to the acceptability of IDC and illustrative quotes.*

A safe and positive use of HD treatment time	<ul style="list-style-type: none"> • “Yes, I found it useful. It made me do some exercise instead of just laying here drinking tea and watching TV, doing jigsaw puzzles.” (Male, mildly frail). • “They bring the bike but first they test you... whether you’re safe to do it and all that.” (Female, mildly frail).
Limited scope and uncertain impact of IDC	<ul style="list-style-type: none"> • “We did cycling, and that was no choice because that’s the only exercise we can do with our legs. You can’t do sit-ups or stand-ups while you are lying down because you’ve got this thing [HD] going on” (Male, moderately frail) • “I thought maybe it helps, I get rid of some problems or maybe you know I am not walking too much...so I say maybe if I do start cycling...you know I can walk...but nothing happened, no nothing.” (Male, severely frail). • “My legs have become stronger, they were wobbly...it's more sturdy now than before. Yet I still have the falls, that I cannot help. But my legs are stronger than they were. I am a bit more agile than I used to be.” (Male, moderately frail). • “It was fine, it was ok, I got on with it. I used to have a laugh but then eventually my knees were just so painful then my [blood] pressure played up a bit.” (Female, vulnerable). • “Blood pressure was coming down. Now I used to take medication for the blood pressure now I don’t take it.” (Male, vulnerable).

372

373 *Outcome acceptability*

374 As indicated by participant quotations in Table 5, the number of outcomes and follow-ups
 375 needed to be reduced and participants had a strong preference for outcomes that could be
 376 collected during HD treatment. Many found the ISWT and STS60 assessments too
 377 challenging. Participants were occasionally uncertain of the purpose of the questionnaires and

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3 378 many reported difficulty quantifying symptom severity or a desire to provide 'anticipated'
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5 379 responses.
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11 381 Maintaining mobility, and the ability to undertake a range of ADLS and social roles were
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13 382 viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative
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15 383 study agreed to complete a falls diary and many reported they preferred falls information to
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17 384 be collected during HD treatment. The majority who had fallen rarely reported them to
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19 385 healthcare professionals, believing that they were an expected consequence of HD or having
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21 386 had experience of their concerns about falls being overlooked. Consequently, falls prevention
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23 387 was not viewed as a key outcome.
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388 Table 5. Categories relating to outcome acceptability and illustrative quotes.

<p>Perceptions of outcome assessments</p>	<ul style="list-style-type: none"> • “It was a bit of a task, too many [outcomes] personally” (Male, mildly frail). • “It’s really helpful if it’s [outcome assessment] done here whilst I am on dialysis. We have got all this free time. Sometimes its five medical appointments a week, Tuesdays and Thursdays [non-dialysis days] become quite precious to me” (Male, vulnerable). • “Do you mean someone would come to my house and do it [complete the functional tests]? I think that would be more doable.” (Female, moderately frail). • “The walking ones [tests] I could make the distance, but the time was ridiculous, they asked me to do it fast. I can’t, I have only got one speed” (Male, vulnerable). • “I am not very good at scores, or you know, what they say about pain, what number it is? I am no good at that. I don’t know what it means. I know it really hurts but I just can’t describe the extent of it. It’s difficult to put it in a number like that” (Female, vulnerable). • “Like all form filling, you can be undecided as to what or how to answer them. Sometimes you don’t, you kind of guess what you should be saying” (Male, mildly frail). 						
<p>Important outcomes</p>	<table border="1"> <tr> <td data-bbox="256 824 459 981"> <p>Maintaining mobility</p> </td> <td data-bbox="459 824 1473 981"> <ul style="list-style-type: none"> • “If you are walking better you are not getting out of breath and that's what does me. I mean I can't walk down this corridor to the ambulance because I am having to stop and get my breath back” (Female, moderately frail). </td> </tr> <tr> <td data-bbox="256 981 459 1272"> <p>Maintaining activities of daily living and social roles</p> </td> <td data-bbox="459 981 1473 1272"> <ul style="list-style-type: none"> • “I don't want to walk miles I just want to do enough to get around...from my chair to my commode or from my commode onto the bed. The only way I can do that is with the rotunda at the minute. I would like to do it with my walking frame” (Female, moderately frail). • “I just want to carry on living and enjoying my life with my [partner] and children, my sisters, and of course all my friends, the church involvement, because I want to enjoy that for absolutely as long as I can” (Male, mildly frail). </td> </tr> <tr> <td data-bbox="256 1272 459 1946"> <p>Falls and falls diaries</p> </td> <td data-bbox="459 1272 1473 1946"> <ul style="list-style-type: none"> • “I don’t fall on a weekly basis... falling over is not something that happens on any sort of regular basis” (Male, moderately frail). • “When I was at the hospital, I told them I had a fall. They don’t want to know. They said, ‘you are perfect, your levels [bloods] are perfect and everything’.” (Male, vulnerable). • “You know I sometimes I forget [to write in the diary]. So, the first days I had written and then I forgot it. And when you forget it then you can’t get the information right.” (Male, severely frail). • “I can’t hold a pen properly, so I am not able to write. [Because of] arthritis they said, because I have got neuropathy and because I am on dialysis phosphate is causing my fingers to sometimes...close up.” (Male, moderately frail). • “If [the researcher is] opposite you and gives you the information, [they’re] going to explain it even better, you know [they] can even ask [the participant] what happened and then they explain to [the researcher] different. But you forget you know the diary it’s very difficult and some of [the participants] won’t ever to know how to use it” (Male, mildly frail). </td> </tr> </table>	<p>Maintaining mobility</p>	<ul style="list-style-type: none"> • “If you are walking better you are not getting out of breath and that's what does me. I mean I can't walk down this corridor to the ambulance because I am having to stop and get my breath back” (Female, moderately frail). 	<p>Maintaining activities of daily living and social roles</p>	<ul style="list-style-type: none"> • “I don't want to walk miles I just want to do enough to get around...from my chair to my commode or from my commode onto the bed. The only way I can do that is with the rotunda at the minute. I would like to do it with my walking frame” (Female, moderately frail). • “I just want to carry on living and enjoying my life with my [partner] and children, my sisters, and of course all my friends, the church involvement, because I want to enjoy that for absolutely as long as I can” (Male, mildly frail). 	<p>Falls and falls diaries</p>	<ul style="list-style-type: none"> • “I don’t fall on a weekly basis... falling over is not something that happens on any sort of regular basis” (Male, moderately frail). • “When I was at the hospital, I told them I had a fall. They don’t want to know. They said, ‘you are perfect, your levels [bloods] are perfect and everything’.” (Male, vulnerable). • “You know I sometimes I forget [to write in the diary]. So, the first days I had written and then I forgot it. And when you forget it then you can’t get the information right.” (Male, severely frail). • “I can’t hold a pen properly, so I am not able to write. [Because of] arthritis they said, because I have got neuropathy and because I am on dialysis phosphate is causing my fingers to sometimes...close up.” (Male, moderately frail). • “If [the researcher is] opposite you and gives you the information, [they’re] going to explain it even better, you know [they] can even ask [the participant] what happened and then they explain to [the researcher] different. But you forget you know the diary it’s very difficult and some of [the participants] won’t ever to know how to use it” (Male, mildly frail).
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389 *Perceptions of a tailored exercise programme*390 *Delivery*

391 There was no universally acceptable setting for exercise delivery (Table 6). Vulnerable and
392 mildly frail participants (CFS 4-5) were particularly open to group-based exercise in the
393 community or gym, which they felt would provide motivation through camaraderie with
394 others. However, access barriers due to HD treatment, complex health needs, and lack of
395 transport were common. Participants also described feeling self-conscious exercising
396 amongst 'normal' people. Home-based exercise was preferred by those with moderate to
397 severe frailty (CFS 6-7) due to easier access, greater flexibility and relevance to their daily
398 activities. Despite this, concerns about lack of space and safety were highlighted by those
399 who lived alone, whilst those with family were concerned about overburdening or injuring
400 them by asking for support.

401 Table 6. Participants perceptions of the facilitators and barriers to group and home-based exercise.

Exercise setting	Facilitators	Barriers
Group community or gym-based exercise	<p>“There is something about the group dynamics, when you try and do it on your own and you can't really focus. It's just so much easier to do as a group than an individual, especially if you have got motivational problems and you're having to do this [dialysis]” (Male, vulnerable)</p> <p>“Better to be in a group, because when you see other people doing it, you just automatically join in and you feel like she can do it why not me?”(Female, mildly frail).</p> <p>“We are all in the same boat. You can say how are you going on this week, you know you are on dialysis, are you finding this OK and you can get notes from them” (Female, severely frail).</p>	<p>“I was lucky enough that my wife was off so she took me and brought me, otherwise transport was a problem, sometimes I used to take a taxi because hospital transport you can't trust it” (Male, moderately frail).</p> <p>“I have only got Tuesday and Thursday and most of the days that cropped up [to attend a falls prevention programme] they are either on a Wednesday or a Friday when I couldn't go because I have dialysis” (Male, mildly frail).</p> <p>“Apparently because of my complex problems and disabilities he [participants GP] doesn't think anyone at the gym is sufficiently qualified to tell me which exercises are best” (Female, moderately frail).</p> <p>“I would love to go to the gym and start sorting myself, but it's just a normal gym where normal keep-fit people go, so I have never ended up there” (Female, vulnerable).</p>
Home-based	<p>“When you are at home exercise is normal it really is. If you are going upstairs to get something you don't think...I am not going up there to get that. You go upstairs and get it because that's part of your everyday life” (Male, moderately frail).</p>	<p>“It's just the room that you have got where you can do exercise...if you haven't got that it's very difficult” (Female, moderately frail).</p> <p>“I can't do anything in the home. There is no-one there, I'm alone, what if anything happens?” (Male, mildly frail).</p> <p>“I am nervous about practising at home because if I couldn't get up, I don't want my husband hurting his back. I shall have to wait until a friend comes around and they could both help me” (Female, moderately frail).</p>

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3 403 *Characteristics of a tailored exercise programme*
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5 404 Irrespective of the setting for delivery, participants identified several key features of a
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7 405 tailored exercise intervention which are summarised in Figure 2.
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13 407 [FIGURE TWO. THE CORE COMPONENTS OF AN ACCEPTABLE EXERCISE
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15 PROGRAMME FOR PEOPLE LIVING WITH FRAILITY AND RECEIVING
16 408 HAEMODIALYSIS TO BE INSERTED HERE]
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21 410 *Preparation*
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23 411 Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and
24
25 412 dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts
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27 413 of exercise (for example breathlessness whilst exercising) were interpreted as worsening
28
29 414 symptoms or damage, and many participants were uncertain if exercise would be suitable or
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31 415 beneficial. They indicated that the reason for exercising needed to be sufficiently compelling.
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33 416 They wanted to know what to expect prior to exercising, and individualised goal setting was
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35 417 advocated to build motivation and appreciate improvements.
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43 419 *Content*
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45 420 Key components described were whole body resistance, aerobic and balance training. Many
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47 421 participants described being unable to get up once they had fallen and felt that practising this
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49 422 was also important. Routine physical activity was viewed as more purposeful than structured
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51 423 exercise 'for the sake of it' and participants spoke of their enjoyment of being outside and
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53 424 engaging in meaningful and physically active hobbies.
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3 426 *Structure*
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5 427 Supervision was viewed as essential to select, teach and progress exercises. Individual
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7 428 tailoring which considered the impact of disability, comorbidities and fluctuating symptoms
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9 429 was important, and a choice of exercises, for example swimming, dancing and yoga, was
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11 430 associated with increased enjoyment and engagement. Moderate to severely frail participants
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13 431 wanted the programme to be progressed in a supportive and collaborative manner. Those who
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15 432 were vulnerable or mildly frail wanted to be ‘pushed’ and progressed in a more assertive
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17 433 manner.
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25 435 Having a companion (typically peers, family or friends) was viewed as helping to overcome
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27 436 access barriers and provide socialisation and mutual motivation. The sharing of experience
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29 437 was also seen as a powerful means of challenging preconceptions about exercise ability,
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31 438 although participants with moderate to severe frailty raised concerns about feeling
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33 439 embarrassed or ‘judged’ if they were less able.
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40 441 **Integrated mixed-methods analyses**
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43 442 The integrated qualitative and quantitative findings suggest that an RCT of IDC is feasible for
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45 443 frail HD patients following adaptation. However, IDC should not be the only intervention
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47 444 offered and the development of a multicomponent programme is warranted (Supplementary
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49 445 material 11).
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56 447 **DISCUSSION**
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3 448 These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to
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5 449 increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was
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7 450 viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest
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9 451 that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity,
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11 452 endurance and functional muscle strength and increase PA behaviour (steps/day), and reduce
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13 453 falls incidence. Despite this, participants described a preference for a multi-component
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15 454 programme that prepared them for exercise, offered variety, companionship and
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17 455 individualised supervision. No single preferred environment for the delivery of this
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19 456 intervention was identified, but appeared to be influenced by frailty grade and individual
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21 457 factors.
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30 459 27% to 89% of secondary outcome measure data were missing, and, overall, this progression
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32 460 criterion was not achieved. Given that secondary measures are often insufficiently powered,
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34 461 reducing the number collected within a future trial may improve completion²⁶. Falls were not
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36 462 of primary importance to participants, and this aligns with SONG-HD data which did not
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38 463 identify falls as a key outcome.²⁷ Our findings suggest that accurately capturing prospective
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40 464 falls data may be challenging due to under-reporting, and yet, retrospective falls data
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42 465 collection does not fully reflect the incidence and impact of falls, particularly those which do
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44 466 not require an ED visit or hospital admission. Given the high incidence of falls in this
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46 467 population, capturing falls data may be important in a future trial, and regular prospective
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48 468 recording of information relating to falls as a part of routine practice at the dialysis unit is
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50 469 recommended, in line with participant feedback.⁵ This would provide both clinicians and
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52 470 researchers with higher quality data for use in both prospective and retrospective studies, and
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54 471 to inform clinical care.
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6 473 Further exploration and validation of meaningful measures for HD patients living with frailty
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8 474 is also warranted. Some of the functional measures (the STS60 and ISWT) included were too
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10 475 challenging. In the absence of a core set of functional outcome measures for older people, or
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12 476 people receiving haemodialysis, we suggest that the SPPB may be the most appropriate and
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14 477 feasible method of capturing information about mobility and function. Although challenges
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16 478 with ceiling effects have been identified, this measure had the lowest levels of non-
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18 479 completion within this study, and has demonstrated good test-retest reliability in HD patients
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20 480 and excellent validity and responsiveness to change following an intervention in older adults.
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22 481 ^{28,29} To date, measures of basic and instrumental ADL ability and participation have rarely
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24 482 been used in exercise studies in an HD population. These outcomes were, however,
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26 483 highlighted as important within this study, and have also been included in guidelines and core
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28 484 outcomes sets for HD and older people, warranting their inclusion in future exercise studies
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30 485 relating to frail HD populations.^{27,30,31}
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487 The results of this study indicate that changes to eligibility criteria and screening processes
488 are required. As only patient participants were interviewed, it was not possible to gain any
489 insight on this aspect of feasibility from the qualitative component. Importantly, the
490 challenges of identifying eligible participants do not appear to be unique to this study and a
491 multicentre trial may be required.³²

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493 Higher proportions of older, female and more severely frail HD patients declined to participate
494 and the qualitative data indicated this was due to negative perceptions relating to participation
495 in both exercise and research. Such findings clearly have implications for the external validity

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3 496 of a future trial and the reach of the intervention at the point of implementation.²⁴ To address
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5 497 this, this study suggests recruitment strategies which utilise effective non-verbal
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7 498 communication skills to build rapport and explore participants' perceptions of the
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9 499 intervention and the research process, and subsequently provide balanced information about
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11 500 the study, may lead to more representative recruitment. A sense of equipoise may be
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13 501 preserved by emphasising altruism, access to potentially enhanced care, and an opportunity to
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15 502 learn about their health (which were all identified as motivators to participation), rather than
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17 503 the potential individual benefits of the intervention itself. Involving families and/or peer
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19 504 supporters who have experience of the study and intervention in the recruitment process and
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21 505 introducing opportunities for participants to observe the exercise intervention may also be
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23 506 beneficial. Ultimately the selection of these strategies will depend upon the resources
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25 507 available and the need to strike a balance between conducting a trial with high internal and
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27 508 external validity and going beyond what is pragmatically possible to engage patients in the
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29 509 intervention at the implementation phase.
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39 511 This study suggests that IDC may reduce the incidence of falls resulting in ED visits and
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41 512 hospital admissions in frail HD patients potentially by attenuating a decline in exercise
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43 513 capacity, physical activity behaviour and function at levels shown to be clinically meaningful
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45 514 in other long-term conditions.^{33,34} This indicates that preventing deterioration may be as
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47 515 valuable, and more attainable, as improving outcomes in a frail population. Despite this, frail
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49 516 participants experienced difficulties achieving the proposed level of exercise and maintaining
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51 517 motivation in the face of varying symptomology. Exercise programmes have a dose-response,
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53 518 and these factors may have reduced participants physical capability to exercise and achieve
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55 519 optimal benefit, despite the overall good level of adherence. Clinical decision support tools
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57 520 have been used in other populations to rationalise exercise prescription, progression and
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3 521 amendment in the presence of varying symptomology, and a similar approach may be
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5 522 beneficial for frail HD patients.³⁵
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11 524 This study indicates that participants desire a multicomponent exercise programme, and
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13 525 require an intervention that addresses their particularly low levels of PA. Whilst step count
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15 526 and time spent in light and moderate PA increased following IDC, these were below PA
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17 527 recommendations for older people.³⁶ To date, PA interventions for HD patients have
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19 528 predominantly centred around walking, which may not be appropriate for those living with
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21 529 frailty.³⁷⁻⁴⁰ This study suggests that functional training (task-orientated exercise which
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23 530 engages multiple muscle groups) and physical activity that focuses on ‘doing more’ of these
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25 531 usual tasks may be more acceptable and efficacious. To date, two studies have employed
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27 532 similar approaches with non-frail HD patients. One study demonstrated significant
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29 533 improvements in lower extremity performance and the other a non-significant improvement
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31 534 in physical function and maintenance of other SF-36 domains compared with the control
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33 535 group^{41,42}. In older people without CKD who are living with frailty, functional training
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35 536 included as part of a multicomponent exercise programme is beneficial across a range of
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37 537 outcomes, including greater ability to rise from the floor following a fall.^{40,43-46} A similar
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39 538 approach to exercise prescription may be warranted in a frail HD population.
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49 540 Numerous barriers and facilitators to exercise were identified within this study, which have
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51 541 implications for the design of a programme. The use of theory is crucial in the development
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53 542 of effective interventions and the behaviour change wheel (BCW) is most frequently cited in
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55 543 the development of interventions in CKD.⁴⁷ Mapping the identified barriers and facilitators
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57 544 to the BCW indicates that ameliorating symptom burden prior to exercise, individualised
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3 545 exercise counselling, and a collaborative, problem-solving approach to exercise education are
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5 546 most likely to encourage and sustain participation.^{47,48} Devising ways in which peer and
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7 547 family involvement can be incorporated into the programme may also increase motivation
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9 548 and opportunity to exercise but should be carefully managed given the potential for negative
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11 549 comparison amongst the frailest patients.
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18 551 A lack of preferred environment for intervention delivery may have implications for a
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20 552 definitive RCT. Exercise interventions require motivation, and limited engagement may
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22 553 negatively influence a trials external and internal validity. Ignoring patient preference is also
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24 554 out of step with clinical practice, where rehabilitation involves shared decision-making.
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26 555 Taken together, these factors have implications for determining treatment effects and future
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28 556 intervention implementation.⁴⁹ There is increasing recognition that novel trial designs may be
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30 557 indicated when evaluating complex interventions and a Partially Randomised Patient
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32 558 Preference Trial, where participants without preference are randomised whilst those with a
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34 559 preference receive their choice, would provide information on both the efficacy of the
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36 560 intervention and the influence of preference.^{49,50}
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43 44 45 562 **Strengths and limitations**

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48 563 To our knowledge, this study is the first to examine the feasibility of an RCT of IDC for frail
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50 564 HD patients and to explore how trial procedures and exercise programmes should be
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52 565 specifically tailored to the needs of this group, from their own perspectives. Key strengths
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54 566 were the use of a validated frailty risk-stratification measure and multiple qualitative methods
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56 567 which provided a form of triangulation.⁵¹ There were, however, challenges to recruiting
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58 568 severely frail participants, and those from a more diverse range of black and minority ethnic
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3 569 groups, to both the trial and the qualitative study. Additionally, the views of clinicians and
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5 570 researchers were not explored. A future RCT should also blind outcome assessors to group
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7 571 allocation to reduce the potential for detection bias. Finally, this study is exploratory and
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9 572 therefore all secondary measures of exercise capacity, function and PROMS should be
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11 573 interpreted with caution, not least due to the high number of participants who did not
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13 574 complete the follow up tests.
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20 576 **Conclusion**

23 577 In summary, this study suggests that a future definitive trial of IDC is feasible within a HD
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25 578 population with a CFS of 4-7 and paying particular attention in the design to those factors
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27 579 mentioned above may facilitate improved rates of eligibility and outcome completion.
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29 580 Outcomes focusing on independence and participation should be the primary outcomes of
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31 581 interest in a future trial. Whilst an exploratory analysis suggests some potential benefits to
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33 582 IDC, a tailored intervention comprising a comprehensive multi-component exercise
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35 583 programme, symptom management, education and behaviour change is better suited to frail
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37 584 HD patients' needs.
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56 590

58 591 **COMPETING INTERESTS**

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2
3 592 The authors have no conflicts of interest to declare.
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35 605 Literature search: HMLY; Research idea and study design: HMLY, JOB; participant
36

37 606 recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC,
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39 607 MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical
40

41 608 analysis: HMLY; supervision and mentorship: SC, HE, SG, SJS, ACS, JOB; manuscript
42

43 609 preparation: HMLY; reviewed final manuscript: all. Each author contributed important
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45 610 intellectual content during manuscript drafting or revision and accepts accountability for the
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47 611 overall work by ensuring that questions pertaining to the accuracy or integrity of any portion
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49 612 of the work are appropriately investigated and resolved. All authors have read and approved
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51 613 the final version
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3 **615 ETHICAL APPROVAL**
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6 616 This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and
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8 617 South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial
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10 618 and the qualitative component respectively
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16 **620 DATA SHARING STATEMENT**
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19 621 The datasets used and analysed during the current study are available from the corresponding
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21 622 author on reasonable request.
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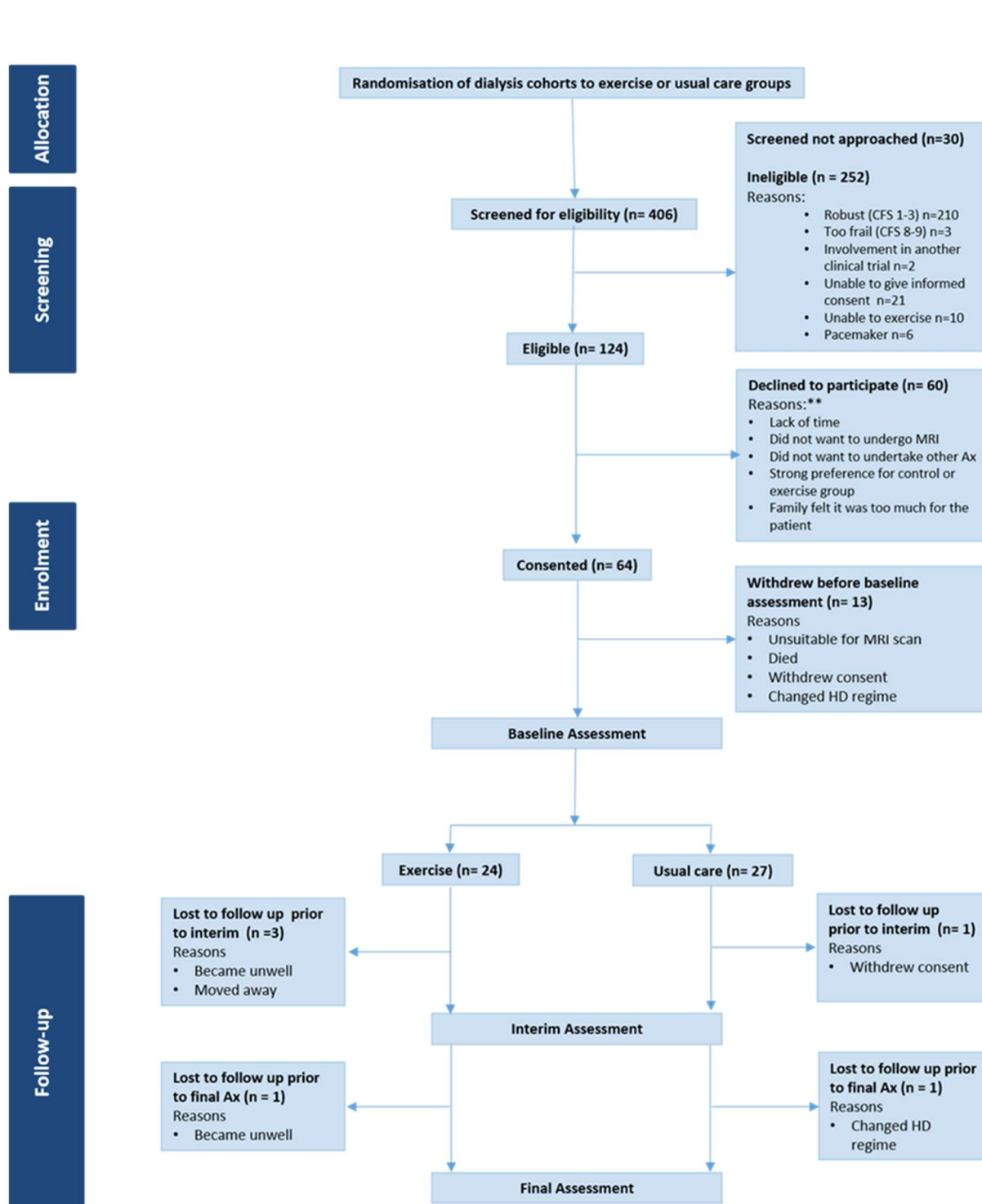
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36 760 Legends to Figures
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39 761 Figure 1. CONSORT
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42 762 Figure 2. The core components of an acceptable exercise programme for people living with
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44 763 frailty and receiving haemodialysis.
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51 765 **SUPPLEMENTARY MATERIAL**
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54 766 Supplementary material 1. Inclusion and exclusion criteria for the CYCLE-HD trial
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56 767 Supplementary material 2. Summary of intervention characteristics, in line with TiDier
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58 768 guidance.
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3 769 Supplementary material 3. *A priori* progression criteria based on the primary feasibility
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5 770 objectives.
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8 771 Supplementary material 4. Patient-reported secondary outcome measures.
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11 772 Supplementary material 5. Interview topic guide questions.
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14 773 Supplementary material 6. Falls summary data and incidence of falls per person years.
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16 774 Supplementary material 7. Changes in exercise capacity and physical function after six
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18 775 months.
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21 776 Supplementary material 8. Changes in physical activity (accelerometry data) after six months.
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24 777 Supplementary material 9. Patient-reported outcomes measures after six months.
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27 778 Supplementary material 10. Baseline demographic and clinical characteristics for the
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29 779 qualitative participants.
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32 780 Supplementary material 11. Joint display of quantitative and qualitative results, with an
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34 781 overall assessment of mixed-methods inferences.
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Abbreviations: Ax, assessment; CFS, Clinical Frailty Scale; HD, haemodialysis.

Preparation for exercise



Trial of exercise

"I would like to know what they expected you to do and err ... instead of going and knowing you can't do it and wasting your time" (Female, moderately frail).



Education and awareness

"You ought to tell them... the goodness in [exercising]... Explain that dialysis takes its toll on your body...so to make sure you are still on the... move you have to do exercises" (Male, moderately frail).



Addressing motivation

"You need a goal, otherwise you might think sod it, I will just give up. But if I got really into it and it was doing me good and I can see the improvement and feel the improvement then yes" (Female, moderately frail).



Addressing symptoms

"When you are getting pain... you can't control, you don't want to do anything. You have got enough pain...and you don't want to create more." (Male, moderately frail).



Challenging perceptions

"No now I can't [exercise], I'm older you see now. I can't manage it, I get very tired you even walking from one room to another, I can't" (Female, mildly frail).



Getting up from the floor

"I am down on the floor I can't get up because... I have not got the strength in my legs or my arms to push myself up. I could probably crawl and try and pull myself up on a chair...but that's the only way. Urm .. if you asked me to get down on my knees and I have got one arm I couldn't get up, I would have to use elbows to get up. I just haven't got the strength in my hands and in my legs... to push." (Female, severely frail).



Resistance exercises

"I can't do much with [my arm], at one point I used to be able to lift my arm right up like I do with this one. But because I have got arthritis in my shoulder it's more difficult. I can still do something with it, things I used to be able to do like holding a potato when I am peeling it I can still do that but I rarely often do it. I think it's because I can't get, I have not got the grip as much...I could get a bit more strength in my left hand, in my left arm" (Female, moderately frail).



Activities of daily living and physically active hobbies

"I don't think I would want to commit to going to the gym or anything like that, but I walk around shopping and [the local supermarket]...is bigger than the one [where I previously lived]" (Male, mildly frail).



Aerobic exercise

"What you are doing on a daily basis has a purpose. Because you definitely do everything, whatever you are doing...for a purpose. There is an end result." (Male, moderately frail).



Balance exercise

"The balance is definitely a good thing because that is something that is a problem for me." (Female, vulnerable).



Support

"I think when you have got somebody who knows the exercises...plus if you are not doing it quite right he can say no you should be balanced that way" (Female, mildly frail).

"If like I say I am struggling with this urm...they will let's go back a little bit for that exercise and we will build it back up again" (Female, severely frail).

"As long as whoever was going to do it could sort of empathise with people who are having the difficulties would be OK. I am like 'I have got loads of problems and you don't have it so you don't know' right?" (Female, vulnerable).



Progression

"It's not going to be like you do it one day and you're going to conquer the whole thing. It's going to take time, it's going to take a couple of...months you know...slowly, slowly, you know" (Male, vulnerable).

"They have got to push you a little bit, yeah OK they can supervise you and suggest things, but I would like it to be more active. I think sometimes that takes... a bit of a sergeant major type to push things beyond what you were comfortable with" (Male, vulnerable).



Companionship

"I think everyone would be able to share different things. Someone could say something and somebody would go 'oh yeah!' Sometimes something that you say surprises someone else when you say it." (Female, vulnerable).

"You don't want to fall because someone will pick you up and that will be embarrassing. It's going to be very hard for me to not bother about them [others exercising]. What are they thinking?" (Female, severely frail).



Enjoyment

"People need to be in the same boat. A thing that comes to me is taking account of people's disabilities, maybe not everyone is at the same level" (Female, moderately frail).

"If someone makes exercise fun I think that makes all the difference." (Female, moderately frail).



Choice

"Ask what exercise would you like to do. If you asked them they would probably turn around and say well I want to go on the treadmill or someone will say I will do cycling and some of them might give up on it" (Male, moderately frail).

Content of the exercise programme

Structure of the programme

Supplementary material 1. Inclusion and exclusion criteria for the *CYCLE-HD* trial.

Inclusion criteria	Exclusion criteria
Prevalent HD patient (> three months)	Unable to participate in current exercise programme due to perceived physical or psychological barriers
Aged 18 years or older	Unable to undergo MRI scanning (metal implants, severe claustrophobia)
Able and willing to give informed consent	Unfit to undertake exercise according to the American College of Sports Medicine (ACSM) guidelines

Supplementary material 2. Summary of intervention characteristics, in line with TiDier guidance.

Description of intervention.		A structured, supervised cycling exercise intervention delivered during in-centre HD.
Rationale.		<ul style="list-style-type: none"> Intradialytic cycling provides aerobic and low-level resistance training, is associated with increased adherence and is most widely used within practice.
What.	Materials provided to participants or used to support intervention delivery.	<ul style="list-style-type: none"> Cycling was delivered using the Moto Med Letto 2 (Medimotion Ltd). Materials: individualised exercise prescription and records of individual training bouts (duration (mins), intensity (RPE), resistance (gear), power output (watts) and energy expenditure (Kcal). General information on the benefits of exercise (posters and leaflets) available across all 3 HD centres.
	Materials used to train intervention providers.	Standardised progression and training protocol used by all providers.
Who (intervention providers).		<ul style="list-style-type: none"> Qualified exercise professionals with experience of delivering exercise to renal patients. All providers were directly involved in the study, and not delivering the sessions as part of a clinical role. Roles included exercise provision, supervision, monitoring and progression.
How (mode of delivery).		One to one, face to face.
Where (location).		Three HD units across the East Midlands, UK.
When and how much	The frequency of delivery.	Thrice weekly during each dialysis session.
	Target intensity of each bout of exercise.	RPE 12-14 (moderate intensity), cadence 60-70 RPM.
	Target duration of each bout of exercise.	At least 30 minutes of continuous exercise.
	The total duration of delivery.	Six months, with a one-month run-in period to achieve the target exercise prescription.
Tailoring.		<ul style="list-style-type: none"> The starting resistance (gear) based on the individual's tolerance. RPE used throughout to monitor and progress the exercise. Interval training was permitted.

Abbreviations: HD, haemodialysis; Kcal, kilocalories; RPE, rating of perceived exertion, RPM, revolutions per minute.

Supplementary material 3. A priori progression criteria based on the primary feasibility objectives.

Eligibility	Stop	Less than 20% of all patients eligible
	Go	More than 50% of all patients eligible
Recruitment	Stop	Less than 25% of eligible patients recruited
	Go	More than 50% of eligible patients recruited
Exercise acceptability	Stop	Less than 30% adherence to the exercise sessions
	Go	More than 70% adherence to the exercise sessions
Outcome acceptability	Stop	Less than 70% outcome measure completion
	Go	More than 80% outcome measure completion
Loss to follow-up	Stop	More than 40% loss to follow-up
	Go	Less than 20% loss to follow-up

Supplementary material 4. Patient-reported secondary outcome measures.

Patient-reported secondary outcome	Construct measured
12-item Short-Form Health Survey Version 2 (SF-12)	Generic health-related quality of life. Higher scores reflect better HRQoL. Scores are presented as a mental and physical component summary score.
Palliative care Outcomes Scale – Renal version (POS-R)	Renal specific measure of symptomology and symptom burden. A global symptom score was calculated by totalling all the scored items within the questionnaire. The mean number of symptoms, symptom severity was also calculated. Higher scores reflect greater symptom burden.
Hospital Anxiety and Depression Scale (HADS)	Emotional distress. A score of ≥ 14 indicates the presence of emotional distress in HD patients
The Exercise Self-Efficacy Scale (ESES)	Exercise confidence. Higher scores reflecting greater self-efficacy.
Dialysis Patient-Perceived Exercise Benefits and Barriers Scale (DPPEBBS)	HD patients' perceptions of benefits and barriers to exercise. Higher scores indicate a greater perception of the benefits of exercise over barriers.
The Dukes Activity Status Index (DASI)	Self-reported physical function. Higher scores indicate higher levels of physical function. The questionnaire was also used to estimate VO_2 peak.

HD, haemodialysis; HRQoL, Health-related quality of life.

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3 *Supplementary material 5. Interview topic guide question.*
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5 Diary
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- 9 1. Can you tell me about how you have been using the diary?
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11 2. If we asked patients to keep diaries like yours as part of a future study, what might help
12 them?
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14 3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell
15 me more about...?
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19 Exercise intervention for frailty and falls
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23 4. For some people exercising helps to prevent falls, make people more able and feel better.
24 How do you feel about exercising?
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26 5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have
27 you seen these bikes?
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29 6. Programmes that are available for other people who fall include things like group exercise
30 and education. What do you think about this?
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32 7. These programmes usually take place at the hospital. What do you think about this?
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34 8. Some people prefer to do their exercise at home. What do you think about this?
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36 9. Where do you think a programme should be run?
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38 10. How often do you think you would be able to exercise?
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40 11. Would you want any support to help you exercise?
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42 12. What might put you off exercising?
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44 13. What questions might you have before you decide to take part or not?
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46 14. If you did take part in some kind of exercise programme, what improvements would you
47 most like to see?
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51 Research
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- 53 15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE
54 study (declined/ took part. If took part completed/dropped out) if patient unsure]
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56 16. What do you think about the information you receive when deciding to take part in a
57 research study?
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3 17. Often researchers ask you to complete some assessments or tests to see if the thing they
4 are studying is effective or not. What do you think would help patients to complete these
5 assessments/ tests?
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8 18. Sometimes people don't complete the research study, which may happen for several
9 reasons [give examples as needed]. What do you think would help keep dialysis from
10 dropping out of research studies?
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12 19. What would you like to happen once you reach the end of the study?
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For peer review only

Supplementary material 6. Falls summary data and incidence of falls per person years.

	Usual care (n=27)	Exercise (n=24)
Number of Falls	11	5
Number (% of group) of non-fallers	19 (70)	20 (83)
Number (% of group) fallers (≥ 1 fall)	8 (30)	4 (17)
Number (% of group) frequent fallers (≥ 2 falls)	3 (11)	1 (4)
Person years	40.5	36
Incidence rate	0.27	0.14

For peer review only

Supplementary material 7. Changes in exercise capacity and physical function after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
ISWT (m)		n	16	15	36 (-12 to 84)
		Baseline	184 ± 130	237 ± 173	
		Final	158 ± 154	248 ± 192	
		Change	-26 ± 68	11 ± 63	
ESWT (secs)		n	14	15	181 (-92 to 453)
		Baseline	347 ± 384	401 ± 375	
		Final	193 ± 304	428 ± 423	
		Change	-153 ± 286	27 ± 413	
STS60 (n)		n	17	15	0 (-5 to 4)
		Baseline	10 ± 12	13 ± 11	
		Final	10 ± 13	13 ± 12	
		Change	0 ± 7	0 ± 6	
SPPB	Total score	n	17	15	0.5 (-0.7 to 2)
		Baseline	7 ± 3	9 ± 3	
		Final	6 ± 2	8 ± 3	
		Change	-1 ± 2	-0.5 ± 1	
	4m walk time (secs)	n	17	15	1 (-1 to 4)
		Baseline	7 ± 6	4 ± 1	
		Final	6 ± 4	5 ± 2	
		Change	1 ± 5	0 ± 1	
	Gait speed (m/s)	n	17	15	0.05 (-0.12 to 0.22)
		Baseline	0.74 ± 0.29	0.96 ± 0.28	
		Final	0.74 ± 0.28	0.91 ± 0.31	
		Change	0.00 ± 0.22	-0.05 ± 0.24	
	STS5 (secs)	n	9	10	5 (-4 to 15)
		Baseline	17 ± 7	16 ± 14	
		Final	23 ± 13	16 ± 10	
		Change	6 ± 11	0 ± 8	

Abbreviations: CI, confidence interval; ESWT, Endurance Shuttle Walk Test; ISWT, Incremental Shuttle Walk Test; m/s, metres per second; Secs, seconds; SPPB, Short Physical Performance Battery; STS5, Sit to Stand Five Repetitions; STS60, Sit to Stand in Sixty Seconds.

Supplementary material 8. Changes in physical activity (accelerometry data) after six months.

	Type of day		Usual Care	Exercise	Difference (95% CI)
Waking wear time (mins)	HD	n	5	10	244 (16 to 473)
		Baseline	891 ± 202	818 ± 183	
		Final	749 ± 105	921 ± 171	
		Change	-142 ± 166	103 ± 204	
	Non-HD	n	5	10	170 (-13 to 353)
		Baseline	893 ± 90	927 ± 216	
		Final	817 ± 134	1022 ± 165	
		Change	-75 ± 201	95 ± 129	
Steps (steps/day)	HD	n	5	10	859 (-825 to 2543)
		Baseline	2252 ± 4210	1373 ± 1080	
		Final	2464 ± 4783	2444 ± 1904	
		Change	211 ± 593	1070 ± 1665	
	Non-HD	n	5	10	888 (-84 to 1861)
		Baseline	3076 ± 5790	2387 ± 1696	
		Final	2645 ± 5284	2845 ± 2117	
		Change	-430 ± 603	458 ± 903	
Sedentary (mins/day)	HD	n	5	10	28 (-284 to 340)
		Baseline	954 ± 338	954 ± 203	
		Final	965 ± 208	992 ± 182	
		Change	10 ± 200	38 ± 287	
	Non-HD	n	5	10	124 (-205 to 454)
		Baseline	1022 ± 357	1103 ± 253	
		Final	912 ± 224	1117 ± 174	
		Change	-110 ± 298	14 ± 269	
Light PA (mins/day)	HD	n	5	10	91 (23 to -158)
		Baseline	125 ± 51	83 ± 42	
		Final	79 ± 39	127 ± 73	
		Change	-46 ± 45	44 ± 62	
	Non-HD	n	5	10	9 (-71 to 91)
		Baseline	145 ± 59	133 ± 50	
		Final	154 ± 99	151 ± 59	
		Change	9 ± 108	18 ± 44	
Moderate PA (mins/day)	HD	n	5	10	13 (-32 to 57)
		Baseline	83 ± 105	29 ± 33	
		Final	85 ± 123	43 ± 55	
		Change	1 ± 52	14 ± 29	
	Non-HD	n	5	10	20 (40 to -79)
		Baseline	79 ± 96	46 ± 61	
		Final	75 ± 112	62 ± 105	
		Change	-4 ± 40	16 ± 55	
Vigorous PA (mins/day)	HD	n	5	10	3 (-1 to 8)
		Baseline	4 ± 9	1 ± 1	
		Final	1 ± 2	1 ± 3	
		Change	-3 ± 7	0 ± 2	
	Non-HD	n	5	10	1 (0 to 2)
		Baseline	3 ± 0	1 ± 4	
		Final	2 ± 5	1 ± 4	
		Change	-1 ± 2	0 ± 0	

Abbreviations: CI, confidence interval; HD, haemodialysis; mins, minutes; PA, physical activity.

Supplementary material 9. Patient-reported outcomes measures after six months.

	Outcome		Usual Care	Exercise	Difference (95% CI)
SF-12	PCS	n	19	19	0 (-4 to 5)
		Baseline	35 ± 9	35 ± 10	
		Final	36 ± 10	36 ± 10	
		Change	1 ± 7	1 ± 7	
	MCS	n	19	19	4 (-3 to 10)
		Baseline	43 ± 15	45 ± 13	
		Final	46 ± 13	45 ± 13	
		Change	4 ± 7	0 ± 12	
HADS	n	20	17	0 (-3 to 4)	
	Baseline	16 ± 10	15 ± 9		
	Final	14 ± 10	13 ± 9		
	Change	-2 ± 5	-2 ± 6		
POS-R	Global severity score	n	20	18	2 (-3 to 7)
		Baseline	19 ± 14	19 ± 14	
		Final	18 ± 14	20 ± 14	
		Change	1 ± 6	-1 ± 9	
	mean severity	n	20	18	0 (0 to 0)
		Baseline	2 ± 1	2 ± 1	
		Final	2 ± 1	2 ± 1	
		Change	0 ± 0	0 ± 0	
	mean number	n	22	16	0 (-1 to 2)
		Baseline	9 ± 4	10 ± 4	
		Final	9 ± 4	10 ± 5	
		Change	0 ± 4	0 ± 2	
ESES	n	19	16	0 (-1 to 1)	
	Baseline	2 ± 2	2 ± 1		
	Final	2 ± 1	2 ± 1		
	Change	0 ± 1	0 ± 1		
DPPEBBS	n	19	15	3 (-4 to 11)	
	Baseline	59 ± 10	59 ± 15		
	Final	61 ± 10	65 ± 7		
	Change	2 ± 7	6 ± 14		
DASI	n	20	18	4.93 (-0.94 to 10.80)	
	Baseline	13.06 ± 12.85	20.29 ± 14.33		
	Final	17.29 ± 14.41	19.60 ± 14.59		
	Change	4.22 ± 9.72	-0.71 ± 7.92		

Abbreviations: CI, confidence interval; DASI, Duke Activity Status Index; DPPEBBS, Dialysis Patients Benefits and Barriers Scale; ESES, Exercise Self efficacy Scale; HADS, Hospital Anxiety and Depression Scale; MCS, mental component summary score; POS-R, Palliative Outcomes Scale Renal, PCS, physical component summary score; VAS, visual analogue scale.

Supplementary material 10. Baseline demographic and clinical characteristics for the qualitative participants.

	N=25	
Age (years)	69±10	
Gender n (%)	Female	13 (52%)
	Male	12 (48%)
Ethnicity n (%)	White background	13 (52%)
	Asian or Asian British	10 (40%)
	Caribbean	1 (4%)
	Not stated	1 (4%)
Diagnosis	Diabetic nephropathy	11 (44%)
	Aetiology uncertain	6 (24%)
	Chronic pyelonephritis	3 (12%)
	Atypical hemolytic uremic syndrome	1 (4%)
	FSGS	1 (4%)
	Henoch-Schönlein Purpura	1 (4%)
	Minimal change nephropathy	1 (4%)
	Polycystic kidney disease	1 (4%)
CCI	6±2	
Time on HD (months)	43 (IQR 16-85)	
CFS n (%)	Vulnerable	9 (36%)
	Mildly frail	5 (20%)
	Moderately frail	8 (32%)
	Severely frail	3 (12%)
Number of falls in the last six months	3 (IQR 2-4)	
Previous transplant n (%)	No	21 (84%)
	Yes	4 (16%)
Active on transplant list n (%)	No	22 (88%)
	Yes	3 (12%)

Abbreviations: CCI, Charlson comorbidity index; CFS, clinical frailty scale; FSGS, Focal segmental glomerulosclerosis; HD, haemodialysis.

Supplementary material 11. Joint display of quantitative and qualitative results, with an overall assessment of mixed-methods inferences.

	Progression criteria	Feasibility trial	Qualitative results	Mixed-methods inferences
Eligibility	STOP <20% GO >50% eligible.	31% patients eligible	No discussion. Patients not involved in screening process	Silence
Recruitment	STOP <25% GO >50% recruited.	52% eligible patients recruited.	<ul style="list-style-type: none"> - Frailer and female participants less likely to be approached despite eligibility and have more concerns about their suitability - Perception that risks outweigh the potential benefits - Recruitment processes could be improved 	Complementary
Retention	STOP >40% GO <20% lost to follow-up.	12% loss to follow-up. Reasons predominantly unavoidable (death, ill-health).	Loss to follow-up attributed to: <ul style="list-style-type: none"> - Illness; - Length of trial; - Study not meeting expectations. 	Complementary
Intervention	STOP <30% GO >70% adherence over six-months.	74% adherence rate across the six-month exercise duration.	<ul style="list-style-type: none"> - IDC good use of time but limited in scope. - Participants felt safe and felt well supported. - Participants described a range of other important exercise components (see Figure 2) 	Complementary
Outcome	STOP <70% GO >80% outcome measure completion.	Up to 89% of secondary outcome measure data missing Collection of falls data challenging.	<ul style="list-style-type: none"> - Number of outcomes measured viewed as excessive. - Outcome testing during HD or at home preferred. - 52% agreed to complete a falls diary, falls not prioritised by participants. - STS60, ESWT and ISWT unsuitable - Researcher support and family involvement may increase outcome measure completion - Outcomes measuring ADLs and participation in social roles prioritised 	Complementary Silence for PA monitoring.

Results from the feasibility trial are colour coded to depict whether they met the 'stop' (red), 'go' (green) or 'change (orange) progression criteria.

Abbreviations: ADLs, activities of daily living; ESWT, Endurance Shuttle Walk Test; IDC, intradialytic exercise; ISWT, Incremental Shuttle Walk Test; PA, physical activity; STS60, sit to stand in sixty seconds.



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	6
	2b	Specific objectives or research questions for pilot trial	6-7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7 and supplementary material 1
	4b	Settings and locations where the data were collected	7-8,10-11
	4c	How participants were identified and consented	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8 and supplementary material 2
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9-11, supplementary materials 3,4 and 5
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	9 and supplementary material 3
Sample size	7a	Rationale for numbers in the pilot trial	8-9

	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	12-13 figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	12-13 figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1 (trial) supplementary material 10 (qualitative)
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Supplementary materials 6-9 and page 15-17
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplementary materials 6-9 and page 15-17
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	17- 26
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P 17
	19a	If relevant, other important unintended consequences	n/a
Discussion			

1	Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	30
2	Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	26-31
3	Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	26-31
4		22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	26-31
5	Other information			
6	Registration	23	Registration number for pilot trial and name of trial registry	4 and 7
7	Protocol	24	Where the pilot trial protocol can be accessed, if available	7
8	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31
9		26	Ethical approval or approval by research review committee, confirmed with reference number	32

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15 Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. 2016;355.

16 *We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important
17 clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological
18 treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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