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

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ABSTRACT

Objectives

Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic exercise is feasible for frail HD patients, and explore how the intervention may be tailored to their needs.

Design

Mixed-methods feasibility.

Setting & participants

Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7 (vulnerable to severely frail) were eligible for the feasibility study.

Interventions

Participants in the exercise group undertook six-months of thrice-weekly, progressive, moderate intensity intradialytic cycling (IDC).

Outcomes

Primary outcomes were related to feasibility. Secondary outcomes were falls incidence, exercise capacity, physical function, physical activity and patient-reported outcomes (PROMS) at baseline and six months. Acceptability of trial procedures and the intervention were explored via diaries and interviews with n=25 frail HD patients who both participated in (n=13, 52%), and declined (n=12, 48%), the trial.

Results

124 (31%) patients were eligible, 64 (52%) consented and 51 (80%) completed a baseline assessment. N=24 (71% male; 59 ± 13 years) dialysed during shifts randomly assigned to exercise and n=27 (81% male; 65 ± 11) assigned to usual care. N=6 (12%) were lost to follow-up. The exercise group completed 74% of sessions. 27 to 89% of secondary outcome data were missing. Frail HD patients outlined several ways to enhance trial procedures. Maintaining ability to undertake activities of daily living and social participation were outcomes of primary importance. Participants desired a varied exercise programme.

Conclusions

A definitive RCT is feasible, however a comprehensive exercise programme may be more efficacious than IDC in this population.

Trial Registration

ISRCTN11299707; ISRCTN12840463

Keywords: feasibility; frailty; exercise; haemodialysis; mixed-methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

Despite this, frailty is not static and evidence suggests that some factors associated with frailty are amenable to change[6]. Whilst the possible mediating role of exercise has been discussed, to our knowledge no original studies have examined the feasibility or effectiveness of an exercise programme for people living with frailty and receiving HD[7]. To date, exercise interventions for HD patients have focused upon intradialytic exercise, most commonly delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about whether this is the most appropriate training stimulus for frail HD patients[8]. In addition, HD treatment can be poorly tolerated by frail patients and therefore IDC may represent an additional stressor to which these patients are particularly vulnerable[9]. European renal best practice guidance highlights a need for studies which identify how exercise programmes should be more specifically tailored to the needs of frail CKD patients[10], yet to date, there has also been no exploration of the needs, barriers and facilitators to exercise from the perspectives of people living with frailty and receiving HD themselves.

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

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

METHODS

Design

A mixed-methods, prospective, randomised feasibility study was conducted alongside concurrent qualitative diaries and interviews (Trial Registration numbers ISRCTN11299707; ISRCTN12840463). The feasibility study was a secondary analysis of the *CYCLE-HD* trial, whose aims and methods are reported elsewhere[11]. The qualitative component was underpinned by a constructivist Grounded Theory approach[12]. All participants provided written informed consent.

Participants

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

Randomisation

HD cohorts were randomised prior to screening, based on a computer-generated randomisation algorithm held by the Robertson Centre for Biostatistics at the University of Glasgow.

Recruitment

Patients were screened for eligibility by their supervising nephrologist. Suitable patients were approached during HD, and the study explained. For the qualitative component, participants who had been involved in the feasibility study were recruited following completion of, or withdrawal from, the trial to prevent contamination.

Exercise intervention

Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance[14]. Briefly, following a one-month run-in, participants in the exercise group undertook thrice-weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC (MOTOmed Letto2, Reck, Germany), for six months[15]. Cycling resistance was progressively increased to maintain RPE in response to exercise adaptation. Both arms continued with usual care HD as described elsewhere[11].

Sample size

Determinations of sample size from a power calculation around a primary outcome are not relevant to a feasibility study and sample sizes of 24-50 are considered sufficient[16]. For the

qualitative component maximum variation sampling was initially used to ensure diversity in frailty status and level of trial participation[12]. As understanding was gained from preliminary analyses, theoretical sampling was used to further recruit participants[12]. A maximum of 30 interviews were planned, but data collection ceased at the point where theoretical categories were saturated and no longer generated new insight (n=25).

Primary outcome measures

The primary feasibility outcomes are presented in supplementary material 3. Judgement regarding feasibility was based upon a set of *a priori* progression criteria. For each criterion, the development of 'stop'(indicating when there are issues with the trial that cannot be resolved) and 'go' thresholds (when there are no issues that may impede the success of a trial) were co-produced by patients, clinicians and researchers[17,18]. Results falling between these thresholds indicated that adaptation to trial procedures may render a definitive RCT viable[18].

Baseline demographic and clinical variables

Demographic and clinical characteristics were gathered from participants' medical notes. The Charlson Comorbidity Index (CCI) was used to estimate the burden of comorbid disease[19].

Secondary outcome measures

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

Information on the number of falls, defined as 'an unexpected event in which the participants come to rest on the ground, floor, or lower-level' which resulted in Emergency Department visits and hospital admissions were collected from baseline to one year following intervention completion from medical records and hospital episode statistics[20].

Field tests of exercise capacity and physical function included the Incremental Shuttle Walk Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60)[11]. Physical activity (PA) was objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc., Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were used to ensure representative data for average daily wear-time, steps per day, and time (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS) moderate (3-6 METS) and vigorous (>6 METS) PA[21]. PROMs collected are outlined in supplementary material 4[11]. All outcomes were collected at baseline and six months.

Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as outlined previously[11].

Diaries and interviews

Participants first completed a prospective falls diary, recognised as the current 'gold standard' for falls data collection, for up to three months to examine the feasibility of this outcome measure within a future definitive RCT[20]. Semi-structured interviews then explored

participants' experiences of: (i) keeping a falls diary; (ii) participating in a trial; and (iii) their perceptions of IDC and a tailored exercise intervention.

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

Data analysis

Descriptive statistics and confidence intervals were used to estimate feasibility outcomes[23]. The percentage of exercise sessions completed was used to establish the acceptability of IDC. Outcome acceptability was determined by quantifying the amount of missing data across secondary outcomes. No imputation was performed to account for missing data. No statistical testing relating to the efficacy of the exercise intervention was undertaken, although the potential benefits of exercise were estimated[23]. For falls, incident rate ratio and 95% confidence intervals were presented. Statistical analyses were performed using SPSS 24 (IBM UK Ltd, UK).

Qualitative analysis was undertaken by HMLY and SG and informed by a constant comparative approach[12]. Transcripts were reviewed, then coded line by line, followed by focused, and then theoretical, coding[12]. NVivo11 software (QSR International Ltd, version

11, 2016) was used to facilitate data management. Finally, qualitative and quantitative results were merged in a 'joint display' to facilitate an overall assessment of feasibility[24].

Patient and public involvement

The patient and public involvement (PPI) group for this study comprised patients of all ages, genders and ethnicities who were living with frailty and receiving HD, and their relatives. They agreed this study was an important priority for further investigation and particularly stressed the need to add the qualitative component. The PPI group were involved early in ethical approval stages and were actively engaged in writing lay summaries and providing patient perspectives on data collection procedures, ethical issues, and the study dissemination plans. They assisted in the preparation of study documentation, interview topic guides and diary keeping materials. During the study, members of the PPI group attended regular steering meetings and were involved in co-producing the progression criteria.

RESULTS

Feasibility study

Eligibility and recruitment

Screening and recruitment took place from March 2015 to 2018, with data collection completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of time or family support and reluctance to undergo outcome testing, or to be randomised.

Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline assessment. N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four (47%) participants received dialysis during shifts randomised to exercise and twenty-seven (53%) during shifts randomised to usual care.

Participant characteristics

Table 1 displays the characteristics of the trial participants at baseline. Groups were well matched across most variables. A lower proportion of participants were female (23.5%) and severely frail (6%) overall.

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, %)	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%)

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

Retention

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

Exercise adherence

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

Table 2 Mean (SD) exercise achieved per session over the six-month duration of the 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

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

Outcome acceptability

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

baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the primary reason for non-completion for all outcomes across all time points.

Secondary outcomes

Summary falls data are presented in supplementary material 6. The crude falls incident rate ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased incidence of falls within the usual care group.

Exercise capacity was maintained in the exercise group, but deteriorated in the usual care group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also increased in the usual care group (suggesting a deterioration in function), but was maintained in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15) (supplementary material 7).

Step count increased in the exercise group by 859 steps/day (95%CI -825 to 2543) on HD days and 888 steps/day (95%CI -84 to 1861) on non-HD days. Whilst sedentary time was increased in the exercise group on all days compared with the usual care group, this appeared to be offset by increases in light PA and moderate PA, and maintenance (albeit of low levels) of vigorous PA versus maintenance or deterioration across the same metrics in the usual care group (supplementary material 8). For PROMs, outcomes were largely unchanged, except for the DASI score, which appeared to deteriorate in the exercise group and increase in the usual care group, resulting in an overall difference in score of 4.93 (95% CI -0.94 to 10.80) and the

mental component summary score of the SF12 which improved in the usual care group, resulting in an overall difference in score of 4 (95% CI -3 to 10). Exercisers appeared to have a greater perception of the benefits of exercise compared with those in the control group (3, 95% CI -4 to 11) (supplementary material 9).

Serious adverse events

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

Qualitative findings

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

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

Feasibility and acceptability of a definitive trial

Eligibility and recruitment

Declining to participate was underpinned by a perception that the trial could worsen overall health, particularly amongst those who had not previously participated in research or had recently commenced HD. Female participants believed that exercise was predominantly for men and that they were already doing enough daily activity, whilst participants living with moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by exercise. Motivators included a sense of altruism, and the perception that participation could provide opportunities to improve individual outcomes; learn about their own health; and access better healthcare. Participants felt that recruitment could be enhanced by the effective use of non-verbal communication, rapport building, and actively involving family members in the recruitment process, as family support was often a prerequisite to participation (Table 3).

Trial retention

The primary reasons for withdrawal were becoming unwell, the duration of the trial and the research not meeting participants expectations. Participants suggested that having a rapport and maintaining regular dialogue with the research team might help retain participants within a future trial (Table 3).

Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative quotes.

The acceptability of IDC

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

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

Outcome acceptability

As indicated by participant quotations in Table 5, the number of outcomes and follow-ups needed to be reduced and participants had a strong preference for outcomes that could be collected during HD treatment. Many found the ISWT and STS60 assessments too challenging. Participants were occasionally uncertain of the purpose of the questionnaires and many reported difficulty quantifying symptom severity or a desire to provide 'anticipated' responses.

Maintaining mobility, and the ability to undertake a range of ADLS and social roles were viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative study agreed to complete a falls diary and many reported they preferred falls information to be collected during HD treatment. The majority who had fallen rarely reported them to healthcare professionals, believing that they were an expected consequence of HD or having had experience of their concerns about falls being overlooked. Consequently, falls prevention was not viewed as a key outcome.

374 *Table 5. Categories relating to outcome acceptability and illustrative quotes.*

Perceptions of a tailored exercise programme

Delivery

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

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

Characteristics of a tailored exercise programme

Irrespective of the setting for delivery, participants identified several key features of a tailored exercise intervention which are summarised in Figure 2.

Preparation

Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts of exercise (for example breathlessness whilst exercising) were interpreted as worsening symptoms or damage, and many participants were uncertain if exercise would be suitable or beneficial. They indicated that the reason for exercising needed to be sufficiently compelling. They wanted to know what to expect prior to exercising, and individualised goal setting was advocated to build motivation and appreciate improvements.

Content

Key components described were whole body resistance, aerobic and balance training. Many participants described being unable to get up once they had fallen and felt that practising this was also important. Routine physical activity was viewed as more purposeful than structured exercise 'for the sake of it' and participants spoke of their enjoyment of being outside and engaging in meaningful and physically active hobbies.

Structure

Supervision was viewed as essential to select, teach and progress exercises. Individual tailoring which considered the impact of disability, comorbidities and fluctuating symptoms was important, and a choice of exercises, for example swimming, dancing and yoga, was

associated with increased enjoyment and engagement. Moderate to severely frail participants wanted the programme to be progressed in a supportive and collaborative manner. Those who were vulnerable or mildly frail wanted to be 'pushed' and progressed in a more assertive manner.

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

Integrated mixed-methods analyses

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

DISCUSSION

These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity, endurance and functional muscle strength and increase PA behaviour (steps/day). Despite

this, participants described a preference for a multi-component programme that prepared them for exercise, offered variety, companionship and individualised supervision. No single preferred environment for the delivery of this intervention was identified but appeared to be influenced by frailty grade and individual factors.

27% to 89% of secondary outcome measure data were missing, and, overall, this progression criterion was not achieved. Given that secondary measures are often insufficiently powered, reducing the number collected within a future trial may improve completion[27]. Falls were not of primary importance to participants, and aligns with the SONG-HD data which did not identify falls as a key outcome[29]. Our findings suggest that accurately capturing prospective falls data may be challenging due to under-reporting, and yet, retrospective falls data collection does not fully reflect the incidence and impact of falls. Given the high incidence of falls in this population, capturing falls data may be important in a future trial, and researcher-led prospective data collection at the dialysis unit is recommended, in line with participant feedback[5]. Further exploration and validation of meaningful measures for HD patients living with frailty is also warranted. Some of the functional measures (the STS60 and ISWT) included were too challenging and measures of independence, rarely used in exercise studies to date, were highlighted as important within this study, and have also been included in guidelines and core outcomes sets for HD and older people[28-30].

The results of this study indicate that changes to eligibility criteria and screening are required. As only patient participants were interviewed, it was not possible to gain any insight on this aspect of feasibility from the qualitative component. Importantly, the challenges of identifying eligible participants do not appear to be unique to this study. Studies of older

people living with frailty highlight that large numbers need to be screened to achieve a 50% recruitment rate, and a multicentre trial may be required[27].

This study suggests that IDC may reduce falls incidence in frail HD patients potentially by attenuating a decline in exercise capacity, physical activity behaviour and function at levels shown to be clinically meaningful in other long-term conditions[31,32]. This indicates that preventing deterioration may be as valuable, and more attainable, as improving outcomes in a frail population. Despite this, frail participants experienced difficulties achieving the proposed level of exercise and maintaining motivation in the face of varying symptomology. Exercise programmes have a dose-response, and these factors may have reduced participants physical capability to exercise and achieve optimal benefit, despite the overall good level of adherence. Clinical decision support tools have been used in other populations to rationalise exercise prescription, progression and amendment in the presence of varying symptomology, and a similar approach may be beneficial for frail HD patients[33].

This study indicates that participants desire a multicomponent exercise programme, and require an intervention that addresses their particularly low levels of PA. Whilst step count and time spent in light and moderate PA increased following IDC, these were below PA recommendations for older people[34]. To date, PA interventions for HD patients have predominantly centred around walking, which may not be appropriate for those living with frailty[35-38]. This study suggests that functional training (task-orientated exercises which engages multiple muscle groups) and physical activity that focuses on ‘doing more’ of these usual tasks may be more acceptable and efficacious. To date, two studies have employed similar approaches with non-frail HD patients. One study demonstrated significant

improvements in lower extremity performance and the other a non-significant improvement in physical function and maintenance of other SF-36 domains compared with the control group[39,40]. In older people without CKD who are living with frailty, functional training included as part of a multicomponent exercise programme is beneficial across a range of outcomes, including greater ability to rise from the floor following a fall [38,41-44]. A similar approach to exercise prescription may be warranted in a frail HD population.

Numerous barriers and facilitators to exercise were identified within this study, which have implications for the design of a programme. The use of theory is crucial in the development of effective interventions and the behaviour change wheel (BCW) is most frequently cited in the development of interventions in CKD[45]. Mapping the identified barriers and facilitators to the BCW indicates that ameliorating symptom burden prior to exercise, individualised exercise counselling, and a collaborative, problem-solving approach to exercise education are most likely to encourage and sustain participation[45,46]. Devising ways in which peer and family involvement can be incorporated into the programme may also increase motivation and opportunity to exercise but should be carefully managed given the potential for negative comparison amongst the frailest patients.

A lack of preferred environment for intervention delivery may have implications for a definitive RCT. Exercise interventions require motivation, and limited engagement may negatively influence a trials external and internal validity. Ignoring patient preference is also out of step with clinical practice, where rehabilitation involves shared decision-making. Taken together, these factors have implications for determining treatment effects and future intervention implementation[47]. There is increasing recognition that novel trial designs may be

indicated when evaluating complex interventions and a Partially Randomised Patient Preference Trial, where participants without preference are randomised whilst those with a preference receive their choice, would provide information on both the efficacy of the intervention and the influence of preference[47,48].

Strengths and limitations

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

Key strengths were the use of a validated frailty risk-stratification measure and multiple qualitative methods which provided a form of triangulation[49]. There were, however, challenges to recruiting severely frail participants to both the trial and the qualitative arms. Additionally, the views of clinicians and researchers were not explored. A future RCT should also blind outcome assessors to group allocation to reduce the potential for detection bias.

Conclusion

In summary, this study suggests that a future definitive trial of IDC is feasible within a HD population with a CFS of 4-7 and paying particular attention in the design to those factors mentioned above may facilitate improved rates of eligibility and outcome completion. Outcomes focusing on independence and participation should be the primary outcomes of interest in a future trial. Whilst an exploratory analysis suggests some potential benefits to IDC, a tailored intervention comprising a comprehensive multi-component programme,

symptom management, education and behaviour change is better suited to frail HD patients' needs.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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AUTHORS CONTRIBUTIONS

Literature search: HMLY; Research idea and study design: HMLY, JOB; participant recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC, MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical analysis: HMLY; supervision and mentorship: SC, HE, SG, SJS, ACS, JOB; manuscript preparation: HMLY; reviewed final manuscript: all. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the final version

ETHICAL APPROVAL

This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial and the qualitative component respectively

DATA SHARING STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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LEGENDS TO FIGURES

Figure 1.CONSORT

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

SUPPLEMENTARY MATERIAL

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

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

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

Supplementary material 4. Patient-reported secondary outcome measures.

Supplementary material 5. Interview topic guide questions.

Supplementary material 6. Incidence of falls per person-year.

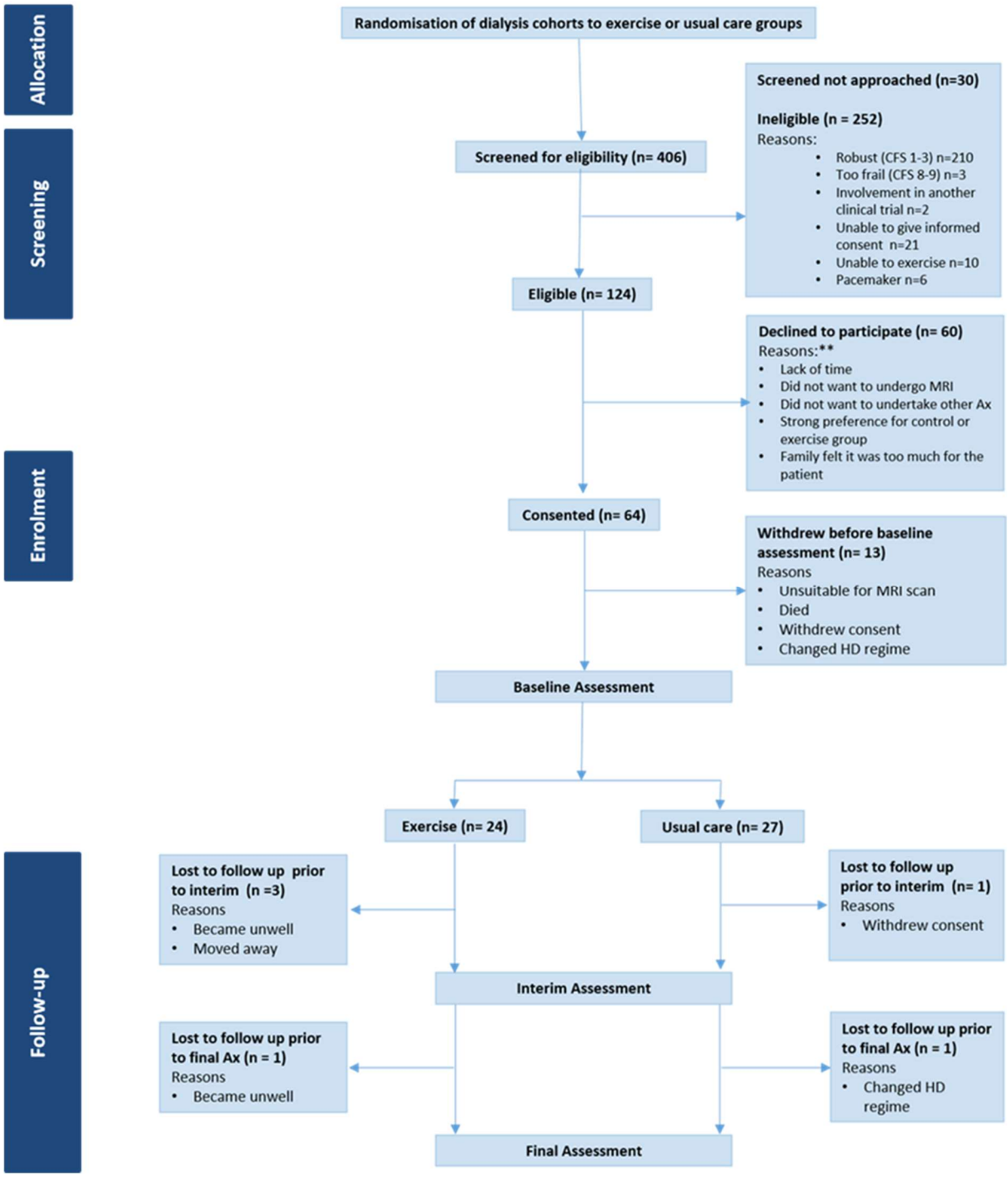
Supplementary material 7. Changes in exercise capacity and physical function after six months.

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

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

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

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



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.		• 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.	• 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).		• 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.		• 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.

Supplementary material 5. Interview topic guide question.

Diary

1. Can you tell me about how you have been using the diary?

2. If we asked patients to keep diaries like yours as part of a future study, what might help them?

3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell me more about…?

Exercise intervention for frailty and falls

4. For some people exercising helps to prevent falls, make people more able and feel better. How do you feel about exercising?

5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have you seen these bikes?

6. Programmes that are available for other people who fall include things like group exercise and education. What do you think about this?

7. These programmes usually take place at the hospital. What do you think about this?

8. Some people prefer to do their exercise at home. What do you think about this?

9. Where do you think a programme should be run?

10. How often do you think you would be able to exercise?

11. Would you want any support to help you exercise?

12. What might put you off exercising?

13. What questions might you have before you decide to take part or not?

14. If you did take part in some kind of exercise programme, what improvements would you most like to see?

Research

15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE study (declined/ took part. If took part completed/dropped out) if patient unsure]

16. What do you think about the information you receive when deciding to take part in a research study?

17. Often researchers ask you to complete some assessments or tests to see if the thing they are studying is effective or not. What do you think would help patients to complete these assessments/ tests?

18. Sometimes people don't complete the research study, which may happen for several reasons [give examples as needed]. What do you think would help keep dialysis from dropping out of research studies?

19. What would you like to happen once you reach the end of the study?

Supplementary material 6. Incidence of falls per patient-year.

	Exercise	**Usual care**
Falls	5	11
Patient-year	36	40.5
Incidence rate	0.14	0.27

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.	- 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: - 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.	- 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.	- 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 materials6-9 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			

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

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.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological 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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ABSTRACT

Objectives

Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic exercise is feasible for frail HD patients, and explore how the intervention may be tailored to their needs.

Design

Mixed-methods feasibility.

Setting & participants

Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7 (vulnerable to severely frail) were eligible for the feasibility study.

Interventions

Participants in the exercise group undertook six-months of thrice-weekly, progressive, moderate intensity intradialytic cycling (IDC).

Outcomes

Primary outcomes were related to feasibility. Secondary outcomes were falls incidence, exercise capacity, physical function, physical activity and patient-reported outcomes (PROMS) at baseline and six months. Acceptability of trial procedures and the intervention were explored via diaries and interviews with n=25 frail HD patients who both participated in (n=13, 52%), and declined (n=12, 48%), the trial.

Results

124 (30%) patients were eligible, 64 (52%) consented and 51 (80%) completed a baseline assessment. N=24 (71% male; 59 ± 13 years) dialysed during shifts randomly assigned to exercise and n=27 (81% male; 65 ± 11 years) assigned to usual care. N=6 (12%) were lost to follow-up. The exercise group completed 74% of sessions. 27 to 89% of secondary outcome data were missing. Frail HD patients outlined several ways to enhance trial procedures. Maintaining ability to undertake activities of daily living and social participation were outcomes of primary importance. Participants desired a varied exercise programme.

Conclusions

A definitive RCT is feasible, however a comprehensive exercise programme may be more efficacious than IDC in this population.

Trial Registration

ISRCTN11299707; ISRCTN12840463

Keywords: feasibility; frailty; exercise; haemodialysis; mixed-methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

Despite this, frailty is not static and evidence suggests that some factors associated with frailty are amenable to change.[6] Whilst the possible mediating role of exercise has been discussed, to our knowledge no original studies have examined the feasibility or effectiveness of an exercise programme for people living with frailty and receiving HD.[7] To date, exercise interventions for HD patients have focused upon intradialytic exercise, most commonly delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about whether this is the most appropriate training stimulus for frail HD patients.[8] In addition, HD treatment can be poorly tolerated by frail patients and therefore IDC may represent an additional stressor to which these patients are particularly vulnerable.[9] European renal best practice guidance highlights a need for studies which identify how exercise programmes should be more specifically tailored to the needs of frail CKD patients[10], yet to date, there has also been no exploration of the needs, barriers and facilitators to exercise from the perspectives of people living with frailty and receiving HD themselves.

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

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

METHODS

Design

A mixed-methods, prospective, randomised feasibility study was conducted alongside concurrent qualitative diaries and interviews (Trial Registration numbers ISRCTN11299707; ISRCTN12840463). The feasibility study was a secondary analysis of the *CYCLE-HD* trial, whose aims and methods are reported elsewhere.[11] The qualitative component was underpinned by a constructivist Grounded Theory approach.[12] All participants provided written informed consent.

Participants

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

The inclusion and exclusion criteria for the qualitative component mirrored the feasibility study and both those involved in the trial, and those who were eligible but declined to participate, were eligible.

Randomisation

HD cohorts were randomised prior to screening, based on a computer-generated randomisation algorithm held by the Robertson Centre for Biostatistics at the University of Glasgow.

Recruitment

Patients were screened for eligibility by their supervising nephrologist. Suitable patients were approached during HD, and the study explained. For the qualitative component, participants who had been involved in the feasibility study were recruited following completion of, or withdrawal from, the trial to prevent contamination.

Exercise intervention

Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance.[16] Briefly, following a one-month run-in, participants in the exercise group undertook thrice-weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC (MOTOmed Letto2, Reck, Germany), for six months.[17] Cycling resistance was progressively increased to maintain RPE in response to exercise adaptation. Both arms continued with usual care HD as described elsewhere.[11]

Sample size

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

Primary outcome measures

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

Baseline demographic and clinical variables

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

Secondary outcome measures

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

Information on the number of falls, defined as 'an unexpected event in which the participants come to rest on the ground, floor, or lower-level' which resulted in Emergency Department visits and hospital admissions were collected from baseline to one year following intervention completion from medical records and hospital episode statistics.[22]

Field tests of exercise capacity and physical function included the Incremental Shuttle Walk Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60).[11] Physical activity (PA) was objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc., Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were used to ensure representative data for average daily wear-time, steps per day, and time (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS) moderate (3-6 METS) and vigorous (>6 METS) PA.[23] PROMs collected are outlined in supplementary material 4.[11] All outcomes were collected at baseline and six months.

Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as outlined previously.[11]

Diaries and interviews

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

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

Data analysis

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

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

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

Patient and public involvement

The patient and public involvement (PPI) group for this study comprised patients of all ages, genders and ethnicities who were living with frailty and receiving HD, and their relatives. They agreed this study was an important priority for further investigation and particularly stressed the need to add the qualitative component. The PPI group were involved early in ethical approval stages and were actively engaged in writing lay summaries and providing patient perspectives on data collection procedures, ethical issues, and the study dissemination plans. They assisted in the preparation of study documentation, interview topic guides and diary keeping materials. During the study, members of the PPI group attended regular steering meetings and were involved in co-producing the progression criteria.

RESULTS

Feasibility study

Eligibility and recruitment

Screening and recruitment took place from March 2015 to 2018, with data collection completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of time or family support and reluctance to undergo outcome testing, or to be randomised. Those who declined to participate had a median age of 73 (IQR 67-8) years. N=35 (58%) were female and n=27 (42%) male. Twenty-five (42%) were classified as vulnerable according to the CFS, n=17 (28%) were mildly frail, n=9 (15%) moderately frail and n=9 (15%) severely frail. Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline assessment. N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four (47%) participants received dialysis during shifts randomised to exercise and twenty-seven (53%) during shifts randomised to usual care.

[FIGURE ONE TRIAL CONSORT TO BE INSERTED HERE]

Participant characteristics

Table 1 displays the characteristics of the trial participants at baseline. Groups were well matched across most variables. A lower proportion of participants were female (23.5%) and severely frail (6%) overall.

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%)

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

Retention

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

Exercise adherence

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

Table 2 Mean (SD) exercise achieved per session over the six-month duration of the 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

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

Outcome acceptability

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

baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the primary reason for non-completion for all outcomes across all time points.

Secondary outcomes

Summary falls data are presented in supplementary material 6. The crude falls incident rate ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased incidence of falls within the usual care group.

Exercise capacity was maintained in the exercise group, but deteriorated in the usual care group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also increased in the usual care group (suggesting a deterioration in function), but was maintained in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15) (supplementary material 7).

Step count increased in the exercise group resulting in an overall difference of 859 steps/day (95%CI -825 to 2543) on HD days and 888 steps/day (95%CI -84 to 1861) on non-HD days. Whilst sedentary time was increased in the exercise group on all days compared with the usual care group, this appeared to be offset by increases in light PA and moderate PA, and maintenance (albeit of low levels) of vigorous PA versus maintenance or deterioration across the same metrics in the usual care group (supplementary material 8). For PROMs, outcomes were largely unchanged, except for the DASI score, which appeared to deteriorate in the exercise group and increase in the usual care group, resulting in an overall difference in score

of 4.93 (95% CI -0.94 to 10.80) and the mental component summary score of the SF12 which improved in the usual care group, resulting in an overall difference in score of 4 (95% CI -3 to 10). Exercisers appeared to have a greater perception of the benefits of exercise compared with those in the control group (3, 95% CI -4 to 11) (supplementary material 9).

Serious adverse events

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

Qualitative findings

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

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

Feasibility and acceptability of a definitive trial

Eligibility and recruitment

Declining to participate was underpinned by a perception that the trial could worsen overall health, particularly amongst those who had not previously participated in research or had recently commenced HD. Female participants believed that exercise was predominantly for men and that they were already doing enough daily activity, whilst participants living with moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by exercise. Motivators included a sense of altruism, and the perception that participation could provide opportunities to improve individual outcomes; learn about their own health; and access better healthcare. Participants felt that recruitment could be enhanced by the effective use of non-verbal communication, rapport building, adaptation to study documentation and actively involving family members in the recruitment process, as family support was often a prerequisite to participation (Table 3).

Trial retention

The primary reasons for withdrawal were becoming unwell, the duration of the trial and the research not meeting participants expectations. Participants suggested that having a rapport and maintaining regular dialogue with the research team might help retain participants within a future trial (Table 3).

Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative quotes.

The acceptability of IDC

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

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

Outcome acceptability

As indicated by participant quotations in Table 5, the number of outcomes and follow-ups needed to be reduced and participants had a strong preference for outcomes that could be collected during HD treatment. Many found the ISWT and STS60 assessments too challenging. Participants were occasionally uncertain of the purpose of the questionnaires and many reported difficulty quantifying symptom severity or a desire to provide 'anticipated' responses.

Maintaining mobility, and the ability to undertake a range of ADLS and social roles were viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative study agreed to complete a falls diary and many reported they preferred falls information to be collected during HD treatment. The majority who had fallen rarely reported them to healthcare professionals, believing that they were an expected consequence of HD or having had experience of their concerns about falls being overlooked. Consequently, falls prevention was not viewed as a key outcome.

388 *Table 5. Categories relating to outcome acceptability and illustrative quotes.*

Perceptions of a tailored exercise programme

Delivery

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

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

Characteristics of a tailored exercise programme

Irrespective of the setting for delivery, participants identified several key features of a tailored exercise intervention which are summarised in Figure 2.

[FIGURE TWO. THE CORE COMPONENTS OF AN ACCEPTABLE EXERCISE PROGRAMME FOR PEOPLE LIVING WITH FRAILTY AND RECEIVING HAEMODIALYSIS TO BE INSERTED HERE]

Preparation

Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts of exercise (for example breathlessness whilst exercising) were interpreted as worsening symptoms or damage, and many participants were uncertain if exercise would be suitable or beneficial. They indicated that the reason for exercising needed to be sufficiently compelling. They wanted to know what to expect prior to exercising, and individualised goal setting was advocated to build motivation and appreciate improvements.

Content

Key components described were whole body resistance, aerobic and balance training. Many participants described being unable to get up once they had fallen and felt that practising this was also important. Routine physical activity was viewed as more purposeful than structured exercise 'for the sake of it' and participants spoke of their enjoyment of being outside and engaging in meaningful and physically active hobbies.

Structure

Supervision was viewed as essential to select, teach and progress exercises. Individual tailoring which considered the impact of disability, comorbidities and fluctuating symptoms was important, and a choice of exercises, for example swimming, dancing and yoga, was associated with increased enjoyment and engagement. Moderate to severely frail participants wanted the programme to be progressed in a supportive and collaborative manner. Those who were vulnerable or mildly frail wanted to be 'pushed' and progressed in a more assertive manner.

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

Integrated mixed-methods analyses

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

DISCUSSION

These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity, endurance and functional muscle strength and increase PA behaviour (steps/day). Despite this, participants described a preference for a multi-component programme that prepared them for exercise, offered variety, companionship and individualised supervision. No single preferred environment for the delivery of this intervention was identified, but appeared to be influenced by frailty grade and individual factors.

27% to 89% of secondary outcome measure data were missing, and, overall, this progression criterion was not achieved. Given that secondary measures are often insufficiently powered, reducing the number collected within a future trial may improve completion.[26] Falls were not of primary importance to participants, and aligns with the SONG-HD data which did not identify falls as a key outcome.[27] Our findings suggest that accurately capturing prospective falls data may be challenging due to under-reporting, and yet, retrospective falls data collection does not fully reflect the incidence and impact of falls, particularly those which do not require an ED visit or hospital admission. Given the high incidence of falls in this population, capturing falls data may be important in a future trial, and regular prospective recording of information relating to falls as a part of routine practice at the dialysis unit is recommended, in line with participant feedback.[5] This would provide both clinicians and researchers with higher quality data for use in both prospective and retrospective studies, and to inform clinical care.

Further exploration and validation of meaningful measures for HD patients living with frailty is also warranted. Some of the functional measures (the STS60 and ISWT) included were too challenging. In the absence of a core set of functional outcome measures for older people, or people receiving haemodialysis, we suggest that the SPPB may be most appropriate and feasible method of capturing information about mobility and function. Although challenges with ceiling effects have been identified, this measure had the lowest levels of non-completion within this study, and has demonstrated good test-retest reliability in HD patients and excellent validity and responsiveness to change following an intervention in older adults.[28,29] To date, more comprehensive measures of basic and instrumental ADL ability and participation have rarely been used in exercise studies. These outcomes were, however, highlighted as important within this study, and have also been included in guidelines and core outcomes sets for HD and older people, warranting their inclusion in future exercise studies relating to frail HD populations.[27,30,31]

The results of this study indicate that changes to eligibility criteria and screening are required. As only patient participants were interviewed, it was not possible to gain any insight on this aspect of feasibility from the qualitative component. Importantly, the challenges of identifying eligible participants do not appear to be unique to this study. Studies of older people living with frailty highlight that large numbers need to be screened to achieve a 50% recruitment rate, and a multicentre trial may be required.[26] Higher proportions older, female and more severly frail HD patients declined to participate whilst the qualitative data indicated this was due to negative perceptions relating to participation in both exercise and research. Such findings clearly have implications for the external validity of a future trial and the reach of the intervention at the point of implementation.[24]

To address this, this study suggests the recruitment strategies which utilise effective non-verbal communication skills to build rapport and explore participants' perceptions of the intervention and the research process, and subsequently provide balanced information about the study, may lead to more representative recruitment. A sense of equipoise may be preserved by emphasising altruism, access to potentially enhanced care, and an opportunity to learn about their health (which were all identified as motivators to participation), rather than the potential individual benefits of the intervention itself. Involving families and/or peer supporters who have experience of the study and intervention in the recruitment process, and introducing opportunities for participants to observe the exercise intervention, may also be beneficial. Ultimately the selection of these strategies will depend upon the resources available and the need to strike a balance between conducting a trial with high internal and external validity and going beyond what is pragmatically possible to engage patients in the intervention at the implementation phase.

This study suggests that IDC may reduce the incidence of falls resulting in ED visits and hospital admissions in frail HD patients potentially by attenuating a decline in exercise capacity, physical activity behaviour and function at levels shown to be clinically meaningful in other long-term conditions.[32,33] This indicates that preventing deterioration may be as valuable, and more attainable, as improving outcomes in a frail population. Despite this, frail participants experienced difficulties achieving the proposed level of exercise and maintaining motivation in the face of varying symptomology. Exercise programmes have a dose-response, and these factors may have reduced participants physical capability to exercise and achieve optimal benefit, despite the overall good level of adherence. Clinical decision support tools

have been used in other populations to rationalise exercise prescription, progression and amendment in the presence of varying symptomology, and a similar approach may be beneficial for frail HD patients.[34]

This study indicates that participants desire a multicomponent exercise programme, and require an intervention that addresses their particularly low levels of PA. Whilst step count and time spent in light and moderate PA increased following IDC, these were below PA recommendations for older people.[35] To date, PA interventions for HD patients have predominantly centred around walking, which may not be appropriate for those living with frailty.[36-39] This study suggests that functional training (task-orientated exercise which engages multiple muscle groups) and physical activity that focuses on 'doing more' of these usual tasks may be more acceptable and efficacious. To date, two studies have employed similar approaches with non-frail HD patients. One study demonstrated significant improvements in lower extremity performance and the other a non-significant improvement in physical function and maintenance of other SF-36 domains compared with the control group.[40,41] In older people without CKD who are living with frailty, functional training included as part of a multicomponent exercise programme is beneficial across a range of outcomes, including greater ability to rise from the floor following a fall.[39,42-45] A similar approach to exercise prescription may be warranted in a frail HD population.

Numerous barriers and facilitators to exercise were identified within this study, which have implications for the design of a programme. The use of theory is crucial in the development of effective interventions and the behaviour change wheel (BCW) is most frequently cited in the development of interventions in CKD[46]. Mapping the identified barriers and facilitators to

the BCW indicates that ameliorating symptom burden prior to exercise, individualised exercise counselling, and a collaborative, problem-solving approach to exercise education are most likely to encourage and sustain participation.[46,47] Devising ways in which peer and family involvement can be incorporated into the programme may also increase motivation and opportunity to exercise but should be carefully managed given the potential for negative comparison amongst the frailest patients.

A lack of preferred environment for intervention delivery may have implications for a definitive RCT. Exercise interventions require motivation, and limited engagement may negatively influence a trials external and internal validity. Ignoring patient preference is also out of step with clinical practice, where rehabilitation involves shared decision-making. Taken together, these factors have implications for determining treatment effects and future intervention implementation.[48] There is increasing recognition that novel trial designs may be indicated when evaluating complex interventions and a Partially Randomised Patient Preference Trial, where participants without preference are randomised whilst those with a preference receive their choice, would provide information on both the efficacy of the intervention and the influence of preference.[48,49]

Strengths and limitations

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

severely frail participants, and those from a more diverse range of black and minority ethnic groups, to both the trial and the qualitative study. Additionally, the views of clinicians and researchers were not explored. A future RCT should also blind outcome assessors to group allocation to reduce the potential for detection bias. Finally, this study is exploratory and therefore all secondary measures of exercise capacity, function and PROMS should be interpreted with caution, not least due to the high number of participants who did not complete the follow up tests.

Conclusion

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

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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AUTHORS CONTRIBUTIONS

Literature search: HMLY; Research idea and study design: HMLY, JOB; participant recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC, MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical analysis: HMLY; supervision and mentorship: SC, HE, SG, SJS, ACS, JOB; manuscript preparation: HMLY; reviewed final manuscript: all. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the final version

ETHICAL APPROVAL

This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial and the qualitative component respectively

DATA SHARING STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Legends to Figures

Figure 1.CONSORT

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

SUPPLEMENTARY MATERIAL

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

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

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

Supplementary material 4. Patient-reported secondary outcome measures.

Supplementary material 5. Interview topic guide questions.

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

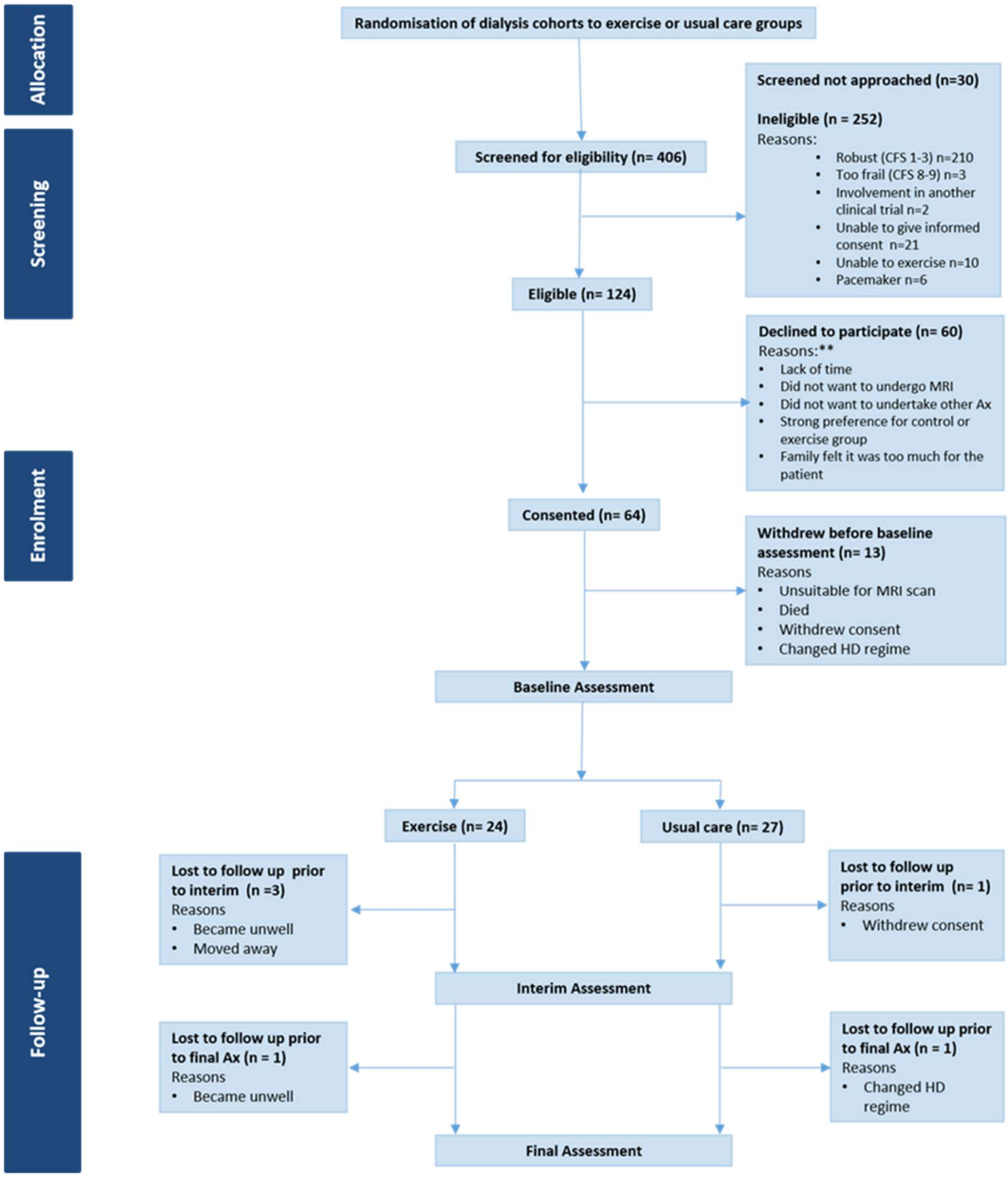
Supplementary material 7. Changes in exercise capacity and physical function after six months.

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

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

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

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



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.		• 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.	• 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).		• 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.		• 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.

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

Supplementary material 5. Interview topic guide question.

Diary

1. Can you tell me about how you have been using the diary?

2. If we asked patients to keep diaries like yours as part of a future study, what might help them?

3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell me more about…?

Exercise intervention for frailty and falls

4. For some people exercising helps to prevent falls, make people more able and feel better. How do you feel about exercising?

5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have you seen these bikes?

6. Programmes that are available for other people who fall include things like group exercise and education. What do you think about this?

7. These programmes usually take place at the hospital. What do you think about this?

8. Some people prefer to do their exercise at home. What do you think about this?

9. Where do you think a programme should be run?

10. How often do you think you would be able to exercise?

11. Would you want any support to help you exercise?

12. What might put you off exercising?

13. What questions might you have before you decide to take part or not?

14. If you did take part in some kind of exercise programme, what improvements would you most like to see?

Research

15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE study (declined/ took part. If took part completed/dropped out) if patient unsure]

16. What do you think about the information you receive when deciding to take part in a research study?

17. Often researchers ask you to complete some assessments or tests to see if the thing they are studying is effective or not. What do you think would help patients to complete these assessments/ tests?

18. Sometimes people don't complete the research study, which may happen for several reasons [give examples as needed]. What do you think would help keep dialysis from dropping out of research studies?

19. What would you like to happen once you reach the end of the study?

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

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.	- 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: - 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.	- 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.	- 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 materials6-9 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			

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

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.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological 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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Exercise for people living with frailty and receiving haemodialysis: a mixed-methods randomised controlled feasibility study.

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ABSTRACT

Objectives

Frailty is highly prevalent in haemodialysis (HD) patients, leading to poor outcomes. This study aimed to determine whether a Randomised Controlled Trial (RCT) of intradialytic exercise is feasible for frail HD patients, and explore how the intervention may be tailored to their needs.

Design

Mixed-methods feasibility.

Setting & participants

Prevalent adult HD patients of the *CYCLE-HD* trial with a Clinical Frailty Scale Score of 4-7 (vulnerable to severely frail) were eligible for the feasibility study.

Interventions

Participants in the exercise group undertook six-months of thrice-weekly, progressive, moderate intensity intradialytic cycling (IDC).

Outcomes

Primary outcomes were related to feasibility. Secondary outcomes were falls incidence measured from baseline to one year following intervention completion, and exercise capacity, physical function, physical activity and patient-reported outcomes (PROMS) measured at baseline and six months. Acceptability of trial procedures and the intervention were explored via diaries and interviews with n=25 frail HD patients who both participated in (n=13, 52%), and declined (n=12, 48%), the trial.

Results

124 (31%) patients were eligible, and of these 64 (52%) consented with 51 (80%) subsequently completing a baseline assessment. N=24 (71% male; 59 ± 13 years) dialysed during shifts randomly assigned to exercise and n=27 (81% male; 65 ± 11 years) shifts assigned to usual care. N=6 (12%) were lost to follow-up. The exercise group completed 74% of sessions. 27 to 89% of secondary outcome data were missing. Frail HD patients outlined several ways to enhance trial procedures. Maintaining ability to undertake activities of daily living and social participation were outcomes of primary importance. Participants desired a varied exercise programme.

Conclusions

A definitive RCT is feasible, however a comprehensive exercise programme may be more efficacious than IDC in this population.

Trial Registration

ISRCTN11299707; ISRCTN12840463

Keywords: feasibility; frailty; exercise; haemodialysis; mixed-methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

Despite this, frailty is not static and evidence suggests that some factors associated with frailty are amenable to change.[6] Whilst the possible mediating role of exercise has been discussed, to our knowledge no original studies have examined the feasibility or effectiveness of an exercise programme for people living with frailty and receiving HD.[7] To date, exercise interventions for HD patients have focused upon intradialytic exercise, most commonly delivered by means of a cycle ergometer (intradialytic cycling, IDC), yet little is known about whether this is the most appropriate training stimulus for frail HD patients.[8] In addition, HD treatment can be poorly tolerated by frail patients and therefore IDC may represent an additional stressor to which these patients are particularly vulnerable.[9] European renal best practice guidance highlights a need for studies which identify how exercise programmes should be more specifically tailored to the needs of frail CKD patients[10], yet to date, there has also been no exploration of the needs, barriers and facilitators to exercise from the perspectives of people living with frailty and receiving HD themselves.

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

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

METHODS

Design

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

Participants

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

The inclusion and exclusion criteria for the qualitative component mirrored the feasibility study and both those involved in the trial, and those who were eligible but declined to participate, were eligible.

Randomisation

HD cohorts were randomised prior to screening, based on a computer-generated randomisation algorithm held by the Robertson Centre for Biostatistics at the University of Glasgow.

Recruitment

Patients were screened for eligibility by their supervising nephrologist. Suitable patients were approached during HD, and the study explained. For the qualitative component, participants who had been involved in the feasibility study were recruited following completion of, or withdrawal from, the trial to prevent contamination.

Exercise intervention

Supplementary material 2 outlines the exercise intervention in line with TIDieR guidance.[16] Briefly, following a one-month run-in, participants in the exercise group undertook thrice-weekly supervised, moderate-intensity (Rating of Perceived Exertion, RPE 12-14) IDC (MOTOmed Letto2, Reck, Germany), for six months.[17] Cycling resistance was progressively increased to maintain RPE in response to exercise adaptation. Both arms continued with usual care HD as described elsewhere.[11]

Sample size

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

Primary outcome measures

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

Baseline demographic and clinical variables

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

Secondary outcome measures

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

Information on the number of falls, defined as 'an unexpected event in which the participants come to rest on the ground, floor, or lower-level' which resulted in Emergency Department visits and hospital admissions were collected from baseline to one year following intervention completion from medical records and hospital episode statistics.[22]

Field tests of exercise capacity and physical function included the Incremental Shuttle Walk Test (ISWT), the Endurance Shuttle Walk Test (ESWT), the Short Physical Performance Battery (SPPB) and the Sit-to Stand in Sixty Seconds (STS60).[11] Physical activity (PA) was objectively measured using the SenseWear Armband (SWA) Pro 3 (BodyMedia, Inc., Pittsburgh PA, USA) for seven consecutive days, including HD. Established criteria were used to ensure representative data for average daily wear-time, steps per day, and time (minutes per day) spent in sedentary (defined as 0-1.5 METS), light (1.6-2.9 METS) moderate (3-6 METS) and vigorous (>6 METS) PA.[23] PROMs collected are outlined in supplementary material 4.[11] All outcomes were collected at baseline and six months.

Serious adverse events (SAEs) were recorded and assessed from baseline to six-months as outlined previously.[11]

Diaries and interviews

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

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

Data analysis

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

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

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

Patient and public involvement

The patient and public involvement (PPI) group for this study comprised patients of all ages, genders and ethnicities who were living with frailty and receiving HD, and their relatives. They agreed this study was an important priority for further investigation and particularly stressed the need to add the qualitative component. The PPI group were involved early in the ethical approval stages and were actively engaged in writing lay summaries and providing patient perspectives on data collection procedures, ethical issues, and the study dissemination plans. They assisted in the preparation of study documentation, interview topic guides and diary keeping materials. During the study, members of the PPI group attended regular steering meetings and were involved in co-producing the progression criteria.

RESULTS

Feasibility study

Eligibility and recruitment

Screening and recruitment took place from March 2015 to 2018, with data collection completed by November 2018. Figure 1 outlines the trial CONSORT. Of the 406 patients screened in the *CYCLE-HD* trial, n=124 (30%, 95% CI 26.1% to 35.3%) were identified as vulnerable to severely frail and therefore eligible for the feasibility study. Sixty-four participants (52%, 95% CI 42.5% to 60.7%) consented. Reasons for declining were lack of time or family support and reluctance to undergo outcome testing, or to be randomised. Those who declined to participate had a median age of 73 (IQR 67-81) years. N=35 (58%) were female and n=27 (42%) male. Twenty-five (42%) were classified as vulnerable according to the CFS, n=17 (28%) were mildly frail, n=9 (15%) moderately frail and n=9 (15%) severely frail. Thirteen (20%, 95% CI 11.3% to 32.2%) participants withdrew prior to baseline assessment. N=51 (80%, 95% CI 67.8% to 88.7%) completed this assessment. Twenty-four (47%) participants received dialysis during shifts randomised to exercise and twenty-seven (53%) during shifts randomised to usual care.

[FIGURE ONE TRIAL CONSORT TO BE INSERTED HERE]

Participant characteristics

Table 1 displays the characteristics of the trial participants at baseline. Groups were well matched across most variables. A lower proportion of participants were female (23.5%) and severely frail (6%) overall.

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%)

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

Retention

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

Exercise adherence

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

Table 2 Mean (SD) exercise achieved per session over the six-month duration of the 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

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

Outcome acceptability

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

baseline, n=27 (57%) at interim and n=40 (89%) at final. For PA data; n=21 (41%) were missing at baseline, and n=26 (58%) were missing at the final assessment. Declining was the primary reason for non-completion for all outcomes across all time points.

Secondary outcomes

Summary falls data are presented in supplementary material 6. The crude falls incident rate ratio (IRR) was 1.95 (95% CI 0.63 to 7.18), suggestive of an almost two-fold increased incidence of falls within the usual care group.

Exercise capacity was maintained in the exercise group, but deteriorated in the usual care group, resulting in an overall difference of 36m (95% CI -12 to 84) in ISWT results and 181 seconds (95% CI -92 to 453) in EWST time. The time taken to complete the STS5 also increased in the usual care group (suggesting a deterioration in function), but was maintained in the exercise group, resulting in an overall difference of 5 seconds (95% CI -4 to 15) (supplementary material 7).

Step count increased in the exercise group resulting in an overall difference of 859 steps/day (95%CI -825 to 2543) on HD days and 888 steps/day (95%CI -84 to 1861) on non-HD days. Whilst sedentary time was increased in the exercise group on all days compared with the usual care group, this appeared to be offset by increases in light PA and moderate PA, and maintenance (albeit of low levels) of vigorous PA versus maintenance or deterioration across the same metrics in the usual care group (supplementary material 8). For PROMs, outcomes were largely unchanged, except for the DASI score, which appeared to deteriorate in the exercise group and increase in the usual care group, resulting in an overall difference in score

of 4.93 (95% CI -0.94 to 10.80) and the mental component summary score of the SF12 which improved in the usual care group, resulting in an overall difference in score of 4 (95% CI -3 to 10). Exercisers appeared to have a greater perception of the benefits of exercise compared with those in the control group (3, 95% CI -4 to 11) (supplementary material 9).

Serious adverse events

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

Qualitative findings

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

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

Feasibility and acceptability of a definitive trial

Eligibility and recruitment

Declining to participate was underpinned by a perception that the trial could worsen overall health, particularly amongst those who had not previously participated in research or had recently commenced HD. Female participants believed that exercise was predominantly for men and that they were already doing enough daily activity, whilst participants living with moderate to severe frailty viewed ageing as an inevitable decline unlikely to be influenced by exercise. Motivators included a sense of altruism, and the perception that participation could provide opportunities to improve individual outcomes; learn about their own health; and access better healthcare. Participants felt that recruitment could be enhanced by the effective use of non-verbal communication, rapport building, adaptation to study documentation and actively involving family members in the recruitment process, as family support was often a prerequisite to participation (Table 3).

Trial retention

The primary reasons for withdrawal were becoming unwell, the duration of the trial and the research not meeting participants expectations. Participants suggested that having a rapport and maintaining regular dialogue with the research team might help retain participants within a future trial (Table 3).

Table 3. Categories relating to trial eligibility, recruitment and retention with illustrative quotes.

Eligibility and recruitment	
Challenges to recruitment	• [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	• "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	• "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	
• "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).	

The acceptability of IDC

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

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

A safe and positive use of HD treatment time	• "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	• "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).

Outcome acceptability

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

many reported difficulty quantifying symptom severity or a desire to provide 'anticipated' responses.

Maintaining mobility, and the ability to undertake a range of ADLS and social roles were viewed as key outcomes for a future trial. Only thirteen (52%) participants in the qualitative study agreed to complete a falls diary and many reported they preferred falls information to be collected during HD treatment. The majority who had fallen rarely reported them to healthcare professionals, believing that they were an expected consequence of HD or having had experience of their concerns about falls being overlooked. Consequently, falls prevention was not viewed as a key outcome.

388 *Table 5. Categories relating to outcome acceptability and illustrative quotes.*

Perceptions of outcome assessments		• "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).
Important outcomes	Maintaining mobility	• "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).
	Maintaining activities of daily living and social roles	• "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).
	Falls and falls diaries	• "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).

Perceptions of a tailored exercise programme

Delivery

There was no universally acceptable setting for exercise delivery (Table 6). Vulnerable and mildly frail participants (CFS 4-5) were particularly open to group-based exercise in the community or gym, which they felt would provide motivation through camaraderie with others. However, access barriers due to HD treatment, complex health needs, and lack of transport were common. Participants also described feeling self-conscious exercising amongst 'normal' people. Home-based exercise was preferred by those with moderate to severe frailty (CFS 6-7) due to easier access, greater flexibility and relevance to their daily activities. Despite this, concerns about lack of space and safety were highlighted by those who lived alone, whilst those with family were concerned about overburdening or injuring 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	"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) "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). "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).	"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). "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). "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). "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).
Home-based	"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).	"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). "I can't do anything in the home. There is no-one there, I'm alone, what if anything happens?" (Male, mildly frail). "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).

Characteristics of a tailored exercise programme

Irrespective of the setting for delivery, participants identified several key features of a tailored exercise intervention which are summarised in Figure 2.

[FIGURE TWO. THE CORE COMPONENTS OF AN ACCEPTABLE EXERCISE PROGRAMME FOR PEOPLE LIVING WITH FRAILTY AND RECEIVING HAEMODIALYSIS TO BE INSERTED HERE]

Preparation

Participants lived with a range of debilitating symptoms, most frequently fatigue, pain and dyspnoea. Often daily activity alone was felt to be enough of a challenge. Common impacts of exercise (for example breathlessness whilst exercising) were interpreted as worsening symptoms or damage, and many participants were uncertain if exercise would be suitable or beneficial. They indicated that the reason for exercising needed to be sufficiently compelling. They wanted to know what to expect prior to exercising, and individualised goal setting was advocated to build motivation and appreciate improvements.

Content

Key components described were whole body resistance, aerobic and balance training. Many participants described being unable to get up once they had fallen and felt that practising this was also important. Routine physical activity was viewed as more purposeful than structured exercise 'for the sake of it' and participants spoke of their enjoyment of being outside and engaging in meaningful and physically active hobbies.

Structure

Supervision was viewed as essential to select, teach and progress exercises. Individual tailoring which considered the impact of disability, comorbidities and fluctuating symptoms was important, and a choice of exercises, for example swimming, dancing and yoga, was associated with increased enjoyment and engagement. Moderate to severely frail participants wanted the programme to be progressed in a supportive and collaborative manner. Those who were vulnerable or mildly frail wanted to be 'pushed' and progressed in a more assertive manner.

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

Integrated mixed-methods analyses

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

DISCUSSION

These results suggest that an RCT of IDC is feasible for frail HD patients with adaptation to increase outcome acceptability and eligibility rates. Adherence to IDC was high and it was viewed as a safe and efficient use of HD treatment time. Secondary outcomes also suggest that, for HD patients with a CFS of 4-7, IDC may mitigate deterioration in exercise capacity, endurance and functional muscle strength and increase PA behaviour (steps/day), and reduce falls incidence. Despite this, participants described a preference for a multi-component programme that prepared them for exercise, offered variety, companionship and individualised supervision. No single preferred environment for the delivery of this intervention was identified, but appeared to be influenced by frailty grade and individual factors.

27% to 89% of secondary outcome measure data were missing, and, overall, this progression criterion was not achieved. Given that secondary measures are often insufficiently powered, reducing the number collected within a future trial may improve completion[26]. Falls were not of primary importance to participants, and this aligns with SONG-HD data which did not identify falls as a key outcome.[27] Our findings suggest that accurately capturing prospective falls data may be challenging due to under-reporting, and yet, retrospective falls data collection does not fully reflect the incidence and impact of falls, particularly those which do not require an ED visit or hospital admission. Given the high incidence of falls in this population, capturing falls data may be important in a future trial, and regular prospective recording of information relating to falls as a part of routine practice at the dialysis unit is recommended, in line with participant feedback.[5] This would provide both clinicians and researchers with higher quality data for use in both prospective and retrospective studies, and to inform clinical care.

Further exploration and validation of meaningful measures for HD patients living with frailty is also warranted. Some of the functional measures (the STS60 and ISWT) included were too challenging. In the absence of a core set of functional outcome measures for older people, or people receiving haemodialysis, we suggest that the SPPB may be the most appropriate and feasible method of capturing information about mobility and function. Although challenges with ceiling effects have been identified, this measure had the lowest levels of non-completion within this study, and has demonstrated good test-retest reliability in HD patients and excellent validity and responsiveness to change following an intervention in older adults.[28,29] To date, measures of basic and instrumental ADL ability and participation have rarely been used in exercise studies in an HD population. These outcomes were, however, highlighted as important within this study, and have also been included in guidelines and core outcomes sets for HD and older people, warranting their inclusion in future exercise studies relating to frail HD populations.[27,30,31]

The results of this study indicate that changes to eligibility criteria and screening processes are required. As only patient participants were interviewed, it was not possible to gain any insight on this aspect of feasibility from the qualitative component. Importantly, the challenges of identifying eligible participants do not appear to be unique to this studyand a multicentre trial may be required.[32]

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

of a future trial and the reach of the intervention at the point of implementation.[24] To address this, this study suggests recruitment strategies which utilise effective non-verbal communication skills to build rapport and explore participants' perceptions of the intervention and the research process, and subsequently provide balanced information about the study, may lead to more representative recruitment. A sense of equipoise may be preserved by emphasising altruism, access to potentially enhanced care, and an opportunity to learn about their health (which were all identified as motivators to participation), rather than the potential individual benefits of the intervention itself. Involving families and/or peer supporters who have experience of the study and intervention in the recruitment process and introducing opportunities for participants to observe the exercise intervention may also be beneficial. Ultimately the selection of these strategies will depend upon the resources available and the need to strike a balance between conducting a trial with high internal and external validity and going beyond what is pragmatically possible to engage patients in the intervention at the implementation phase.

This study suggests that IDC may reduce the incidence of falls resulting in ED visits and hospital admissions in frail HD patients potentially by attenuating a decline in exercise capacity, physical activity behaviour and function at levels shown to be clinically meaningful in other long-term conditions.[33,34] This indicates that preventing deterioration may be as valuable, and more attainable, as improving outcomes in a frail population. Despite this, frail participants experienced difficulties achieving the proposed level of exercise and maintaining motivation in the face of varying symptomology. Exercise programmes have a dose-response, and these factors may have reduced participants physical capability to exercise and achieve optimal benefit, despite the overall good level of adherence. Clinical decision support tools have been used in other populations to rationalise exercise prescription, progression and

amendment in the presence of varying symptomology, and a similar approach may be beneficial for frail HD patients.[35]

This study indicates that participants desire a multicomponent exercise programme, and require an intervention that addresses their particularly low levels of PA. Whilst step count and time spent in light and moderate PA increased following IDC, these were below PA recommendations for older people.[36] To date, PA interventions for HD patients have predominantly centred around walking, which may not be appropriate for those living with frailty.[37-40] This study suggests that functional training (task-orientated exercise which engages multiple muscle groups) and physical activity that focuses on 'doing more' of these usual tasks may be more acceptable and efficacious. To date, two studies have employed similar approaches with non-frail HD patients. One study demonstrated significant improvements in lower extremity performance and the other a non-significant improvement in physical function and maintenance of other SF-36 domains compared with the control group[41,42]. In older people without CKD who are living with frailty, functional training included as part of a multicomponent exercise programme is beneficial across a range of outcomes, including greater ability to rise from the floor following a fall.[40,43-46] A similar approach to exercise prescription may be warranted in a frail HD population.

Numerous barriers and facilitators to exercise were identified within this study, which have implications for the design of a programme. The use of theory is crucial in the development of effective interventions and the behaviour change wheel (BCW) is most frequently cited in the development of interventions in CKD. [47] Mapping the identified barriers and facilitators to the BCW indicates that ameliorating symptom burden prior to exercise, individualised

exercise counselling, and a collaborative, problem-solving approach to exercise education are most likely to encourage and sustain participation.[47,48] Devising ways in which peer and family involvement can be incorporated into the programme may also increase motivation and opportunity to exercise but should be carefully managed given the potential for negative comparison amongst the frailest patients.

A lack of preferred environment for intervention delivery may have implications for a definitive RCT. Exercise interventions require motivation, and limited engagement may negatively influence a trials external and internal validity. Ignoring patient preference is also out of step with clinical practice, where rehabilitation involves shared decision-making. Taken together, these factors have implications for determining treatment effects and future intervention implementation.[49] There is increasing recognition that novel trial designs may be indicated when evaluating complex interventions and a Partially Randomised Patient Preference Trial, where participants without preference are randomised whilst those with a preference receive their choice, would provide information on both the efficacy of the intervention and the influence of preference.[49,50]

Strengths and limitations

To our knowledge, this study is the first to examine the feasibility of an RCT of IDC for frail HD patients and to explore how trial procedures and exercise programmes should be specifically tailored to the needs of this group, from their own perspectives. Key strengths were the use of a validated frailty risk-stratification measure and multiple qualitative methods which provided a form of triangulation.[51] There were, however, challenges to recruiting severely frail participants, and those from a more diverse range of black and minority ethnic

groups, to both the trial and the qualitative study. Additionally, the views of clinicians and researchers were not explored. A future RCT should also blind outcome assessors to group allocation to reduce the potential for detection bias. Finally, this study is exploratory and therefore all secondary measures of exercise capacity, function and PROMS should be interpreted with caution, not least due to the high number of participants who did not complete the follow up tests.

Conclusion

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

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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AUTHORS CONTRIBUTIONS

Literature search: HMLY; Research idea and study design: HMLY, JOB; participant recruitment: HMLY, DS, PH, DC, MPMGB, JOB, CG; data acquisition: HMLY, DS,PH,DC, MPMGB,CG WJ, MC; clinical governance: JOB; data analysis: HMLY, SG; statistical analysis: HMLY; supervision and mentorship: SC, HE, SG, SJS, ACS, JOB; manuscript preparation: HMLY; reviewed final manuscript: all. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the final version

ETHICAL APPROVAL

This study was approved by the East Midlands (Northampton; REC ref: 14/EM/1190) and South West (Bristol; REC ref: 17/SW/0048) NHS Research Ethics Committees for the trial and the qualitative component respectively

DATA SHARING STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Legends to Figures

Figure 1.CONSORT

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

SUPPLEMENTARY MATERIAL

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

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

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

Supplementary material 4. Patient-reported secondary outcome measures.

Supplementary material 5. Interview topic guide questions.

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

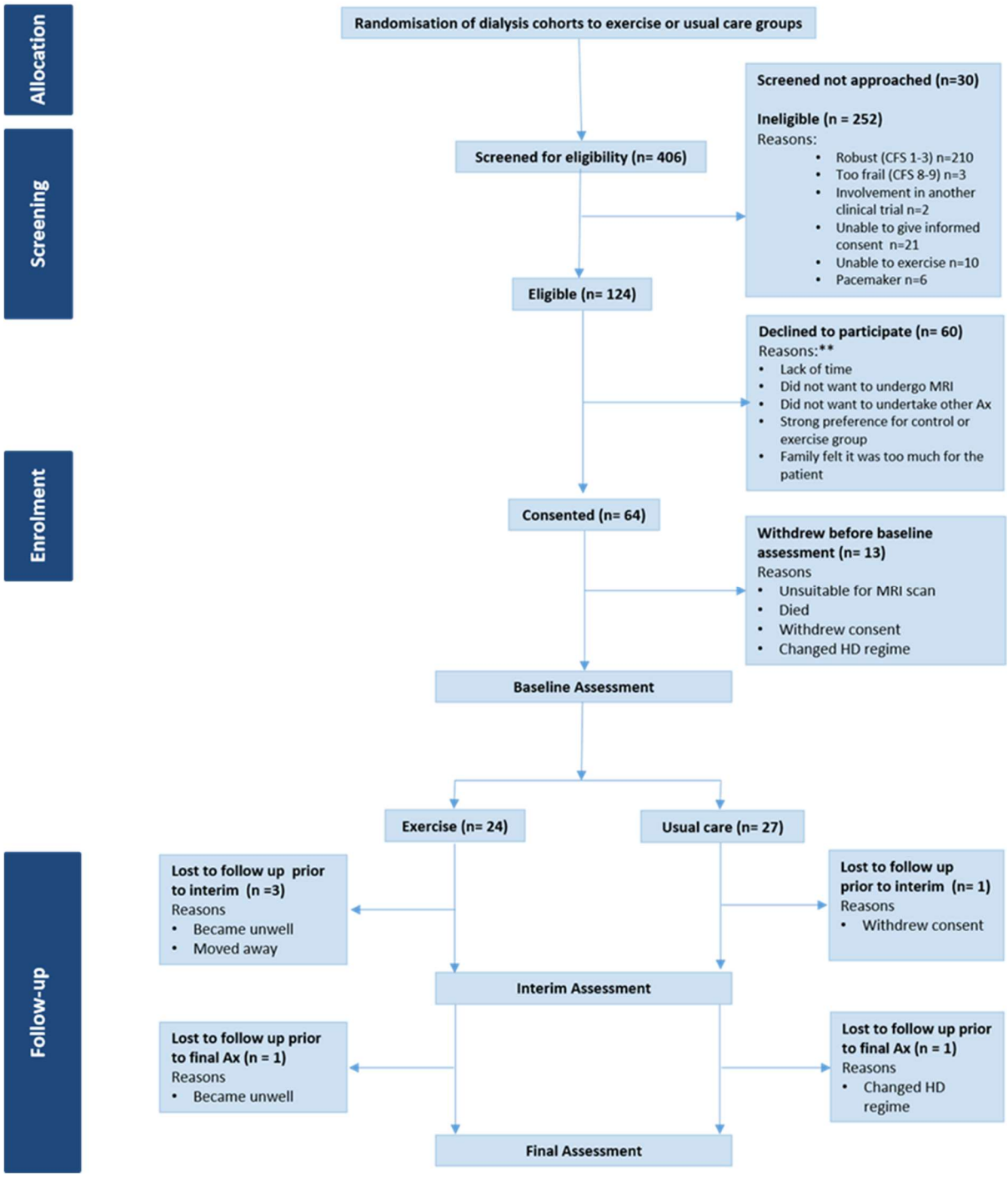
Supplementary material 7. Changes in exercise capacity and physical function after six months.

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

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

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

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



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.		• 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.	• 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).		• 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.		• 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.

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

Supplementary material 5. Interview topic guide question.

Diary

1. Can you tell me about how you have been using the diary?

2. If we asked patients to keep diaries like yours as part of a future study, what might help them?

3. [If applicable] I've had an opportunity to have a look through your diary. Could you tell me more about…?

Exercise intervention for frailty and falls

4. For some people exercising helps to prevent falls, make people more able and feel better. How do you feel about exercising?

5. Cycling during dialysis is thought to be a good way to exercise if you are on dialysis. Have you seen these bikes?

6. Programmes that are available for other people who fall include things like group exercise and education. What do you think about this?

7. These programmes usually take place at the hospital. What do you think about this?

8. Some people prefer to do their exercise at home. What do you think about this?

9. Where do you think a programme should be run?

10. How often do you think you would be able to exercise?

11. Would you want any support to help you exercise?

12. What might put you off exercising?

13. What questions might you have before you decide to take part or not?

14. If you did take part in some kind of exercise programme, what improvements would you most like to see?

Research

15. Have you ever been involved in research before? [Could tailor to involvement in CYCLE study (declined/ took part. If took part completed/dropped out) if patient unsure]

16. What do you think about the information you receive when deciding to take part in a research study?

17. Often researchers ask you to complete some assessments or tests to see if the thing they are studying is effective or not. What do you think would help patients to complete these assessments/ tests?

18. Sometimes people don't complete the research study, which may happen for several reasons [give examples as needed]. What do you think would help keep dialysis from dropping out of research studies?

19. What would you like to happen once you reach the end of the study?

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

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.	- 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: - 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.	- 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.	- 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 materials6-9 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			

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

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.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological 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.