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A randomized factorial mixed-method pilot study of aerobic and resistance exercise in hemodialysis patients: *DIALY-SIZE*!

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Objectives

For people with end-stage renal disease requiring hemodialysis exercise can improve aspects of quality of life (QoL). However, the relative benefits and risks of different types of exercise in this population is unknown. Therefore, this pilot study aimed to evaluate the feasibility of a main study evaluating the efficacy of cycling and resistance exercise each performed during the hemodialysis treatment on QoL.

Methods

In this factorial (2 x 2) pilot trial, 31 hemodialysis patients were randomized to cycling, resistance, cycling and resistance, or stretching (an attention control). Feasibility was defined a priori by criteria on recruitment, fidelity to the protocol, and patient response to the intervention. To better understand feasibility, we conducted interviews with dialysis unit staff and trial participants. As secondary outcomes, we estimated the main effect of cycling and weights each compared with control on QoL, physical function, and strength.

Findings

We exceeded the target accrual of 28 subjects over 12 weeks. Irrespective of exercise group allocation, adherence was high: of the 1,038 training sessions offered, 87% were initiated, and over 80% of exercise sessions were performed as per protocol. Progression based on perceived exertion, individual instruction, and interactions with the kinesiologist facilitated acceptability across all exercise groups. Using an attention control, measures of contamination and attrition were low. Important barriers to staff readiness for IDE were initial safety and workflow concerns, unit workload, and onerous data collection. Secondary outcomes were not statistically significant. Adverse events were low and did not increase with a higher volume of exercise.

Conclusions

The main study is feasible with minor modifications. In addition to practical assistance, involvement from unit staff could increase patient participation and improve trial implementation. Strategies to increase acceptability of the intervention for staff include improving workflow integration and using a pre-study demonstration phase to introduce the intervention.

Trial registration: ClinicalTrials.gov NCT02234232

Strengths and limitations of this study

- To our knowledge, this work is the first to include qualitative methods in evaluating the design of an exercise trial in hemodialysis patients.
- Understanding patient and dialysis unit staff perspectives on trial processes and the intervention was critical in identify barriers to trial implementation and for purposing strategies to improve these.
- Detailed information on aspects of trial delivery contributes useful knowledge to the renal exercise literature on how key methodological and practical limitations could be feasibly improved in order to increase trial quality, relevance, and potentially effectiveness.
- Due to limited sample size, we could not triangulate patients' experiences of intervention factors by high or low adherence.
- Our focus was on identifying the factors that influenced trial implementation and how these factors would influence the longer-term sustainability of the intervention is not clear.

INTRODUCTION

While hemodialysis (HD) is a life-sustaining therapy for people with end-stage renal disease (ESRD), it is associated with low quality of life (QoL) [1,2] and a marked decline in functional status. [3] Although the benefits of exercise in this population have been recognized, few studies have evaluated how different types of exercise can influence QoL, and the majority of interventions have evaluated aerobic exercise.[4,5] How to most effectively engage patients in the optimal exercise prescription and achieve the desired outcome while minimizing risk, is critical to increasing patient participation.

Many generic QoL scales used in exercise studies in people with ESRD address the individual's perception of their ability to meet the demands of everyday living. However, performance of daily tasks is more dependent on musculoskeletal fitness than aerobic capacity.[6,7] In the elderly non-ESRD population,[6,8] and in people with congestive heart failure (CHF),[9] resistance training is a promising means of improving QoL and decreasing disability. However, whether resistance training confers specific benefits relevant to aspects of QoL in people with ESRD is not known.

The aim of our future multicenter study is to evaluate the effect of two types of exercise (cycling and resistance) each compared to control and performed during the HD treatment (intradialytic exercise, [IDE]) on QoL and physical performance using a randomized factorial design. Prior to proceeding with this main study, a pilot was warranted to evaluate the feasibility of the design. Although delivering exercise during HD has been associated with greater adherence compared to a home-based exercise program,[10] few pilot studies have rigorously evaluated the feasibility or the integrity of trial implementation and we are not aware of any studies that have included

qualitative methods to provide a more comprehensive understanding of the implementation process.[11]

METHODS

Study design

In this mixed-methods study of a single-center, randomized, factorial (2 x 2) trial, and qualitative interviews with RCT participants and dialysis unit staff, we evaluated domains of feasibility a priori: recruitment, fidelity to the study protocol, and the response of participants and dialysis unit staff to the intervention. In a secondary analysis, we explored differences in QoL, physical function, and strength. The two factors evaluated were aerobic exercise (cycling) and resistance exercise (leg weights). HD patients were randomized to one of four groups: cycling, leg weights, combined leg weights and cycling, or stretching (an attention control). All exercises were performed during HD at each thrice-weekly dialysis session over 12 weeks (36 sessions). The Health Research Ethics Board at the University of Alberta approved this study. The study protocol was registered under NCT02234232.

Setting and participants

The trial setting was an outpatient dialysis unit in Edmonton, Canada that serves approximately 110 patients. A study coordinator recruited participants during their HD sessions. Inclusion criteria were: adult (age ≥18); dialysis dependent for ≥ 3 consecutive months; receiving ≥ 3 dialysis treatments per week; mobile (any distance, walking aid permitted); at least one non-prosthetic limb; and capable of providing consent. Exclusion criteria were: currently enrolled in a clinical trial; missing an average of more than 2 dialysis sessions per month; planned move or modality change within the next 4 months; currently enrolled in a structured exercise program;

scheduled hospitalization for > 1 week; unstable during HD; and any uncontrolled medical condition that would preclude participation in a low/moderate intensity exercise program.[12]

Randomization and blinding

Participants were randomized on a 1:1:1:1 ratio using a computerized randomization procedure with permuted blocks of eight and twelve. Allocation was concealed in serially numbered, opaque, sealed envelopes. The randomization list was generated by the statistician and kept in a locked cabinet. Given the open setting of the dialysis unit and the nature of the intervention, it was not logistically possible to blind the participants or the kinesiologist to treatment allocation. Therefore, participants and HD unit staff were blinded to the study hypothesis. Patients were informed that they would be randomized to one of four different exercise regimens; a stretching exercise group served as the attention control. A blinded assessor performed outcome assessments at 12 weeks.

Exercise intervention

A kinesiologist instructed all participants on how to perform exercises and supervised most of the participants' thrice-weekly exercise sessions. When study staff were not present, dialysis unit staff assisted patients with equipment and completed trial documentation. All participants were instructed on how to use rating of perceived exertion (RPE) with the Borg scale (6-20).[13] The intensity of exercise for the aerobic, resistance, and combined intervention groups was prescribed at a level of 12-14 or "somewhat hard" on the Borg (RPE) scale and a RPE level of 8-9 ("very light") for the stretching group.

Aerobic intervention

Each session included a five-minute warm-up and cool-down on the cycle ergometer at an RPE of 9-11. The cycling protocol started with 15 minutes of cycling with time increased by 2.5 minutes each week. The resistance was adjusted to maintain the target RPE. One of two types of cycle ergometers were used according to compatibility with the type of dialysis chair: the Monark 881E cycle (Health Care International, Langley, WA) or the TherapyTrainer (Interactive Motivation, Greely, CO).

Resistance intervention

Ankle weights (Fabrication Enterprises, White Plains, NY) were used for knee extension, knee flexion, and hip flexion. A Theraband (The Hygenic Corporation, Akron, OH) was used for hip abduction. Each session included a warm-up of one set of the four exercises against gravity. Based on RPE, exercises progressed from one set of 10-15 repetitions up to three sets. Weight or resistance was increased when the patient's RPE was less than target.

Combined intervention

Participants in the combined training group performed the full resistance exercise program followed by the complete cycling program.

Attention control

To equalize the effect of co-interventions,[14] the control group performed a non-progressive stretching routine during dialysis. Participants performed two sets each of four exercises: pelvic tilts, gluteal stretch, calf, and hamstring stretch. A TheraBand Stretch Strap (The Hygenic Corporation, Akron, OH) was used for the calf and hamstring stretches.

Data collection

Clinical data were collected at baseline via interviews with participants and chart review. Survey data, questionnaires, and tests of physical performance were performed at baseline and at 12 weeks. At each session, the following data was recorded on exercise data collection forms (DCFs): pre- and post-exercise blood glucose (for diabetics), heart rate (HR), blood pressure (BP), reason for exercise non-participation and early termination, if applicable. During exercise, HR, BP, and RPE were documented every five minutes. Data on adverse events (AEs) were collected via interview at each exercise session with the kinesiologist and by chart review.

Primary outcomes

The primary outcome of feasibility was defined by a priori criteria (Table 2) and focused on the following: recruitment (rate of accrual, reason for non-participation); fidelity to the protocol (dropout, adherence); response to the intervention (physical activity level outside of the dialysis unit, adoption of the other group's exercise [contamination]), and acceptability of the intervention.

Recruitment

Previous intradialytic exercise trials report 20-46% of screened patients were randomized.[15–18] We estimated that approximately 85% of the 110 patients in this unit would be available for screening and targeted recruiting 28 subjects. Based on the assumption that interested patients may already have preferences concerning exercise that would make randomization undesirable, unwillingness to be randomized to exercise type was selected as a feasibility criterion. Reason for nonparticipation in the trial was based on self-report.

Fidelity to the protocol

Based on dropout rates from exercise RCTs in people with chronic kidney disease, we defined a high dropout as ≥ 25% of the study population.[4] Any participant who left the study at any time

prior to completing the 12-week exercise program was defined as a dropout. Adherence was measured to assess patients' willingness to participate in IDE and to ascertain if the exercises were performed as per protocol (Table 2).

Response to the intervention

Acceptability of the exercises was defined as ≥50% of participants reporting that they would like to continue their current IDE program after study close. The change in physical activity performed outside of dialysis time was measured by self-reported questionnaire and using the Human Activity Profile (HAP).[19] To evaluate whether any participants adopted the other group's intervention (contamination) outside of dialysis time, patients' completed questionnaires on the types of activities performed in their leisure time at baseline at 12–weeks.

Qualitative interviews

Detailed information on participants and data collection methods can be found elsewhere.[20] To evaluate barriers to IDE implementation and to inform the content of staff in servicing, we interviewed dialysis unit staff three months prior to the start of the trial. To better understand the feasibility of unit staff participation in the delivery of the trial, unit staff members were also interviewed four months into the six-month trial. Unit staff were eligible to participate if the RCT directly affected their workflow and if they had worked in the unit during the trial. Interviews with RCT participants were conducted post trial participation. All RCT participants were eligible if they were capable of sharing their experiences. Interviews were semi-structured with open-ended questions followed by specific prompts on aspects of feasibility. All interviews were audiotaped and transcribed verbatim. For this analysis, interviews were coded using predetermined categories corresponding to our areas of feasibility and analyzed to yield a descriptive summary of study findings.

Secondary outcomes

Secondary outcomes were: QoL, (the physical component summary, [PCS] and the mental component summary [MCS]); tests of physical performance (Short physical performance battery, 30-second sit-to-stand test, and six-minute walk); an objective measure of strength; and AEs. Testing was carried-out at baseline and at 12 weeks, pre-HD on their scheduled HD day.

Quality of life

Participants completed The Kidney Disease Quality of Life Short Form (KDQOL-SF 36).[21] Item scores range from 0-100, with higher scores being more favorable. For this pilot, only the mean difference in PCS and MCS are reported.

Tests of physical performance

We used a range of tests to measure physical performance of the lower extremities. The Short physical performance battery (SPPB) includes: strength (five chair stands), endurance (4-meter gait speed) and balance (side-by-side, semi-tandem, and tandem). Each component is scored from 0 to 4 and is summed SPPB scores between 0 (poor) and 12 (best) performance.[22] The 6-minute walk test (6MWT) was used as a measure of aerobic capacity (distance walked reported in meters) and was performed according to recommendations from the American Thoracic Society.[23] To avoid a ceiling effect and to test muscle endurance, the number of complete getting-up and sitting-down repetitions performed in 30 seconds (STS 30 seconds) was also tested.[24] Muscle strength was measured with the one repetition maximum (1-RM) test using a bilateral leg extension machine for the quadriceps.[25]

Adverse events

AEs were defined a priori and categorized as serious (death, cardiac event, hospitalization, disability, or any life-threatening event) or other (musculoskeletal injury, hypoglycemia, hypotension, hypertensive urgency [>200 mm Hg systolic or 110 mmHg diastolic], loss of consciousness, dialysis access complications, or any intervention by HD unit staff beyond minimal ultrafiltration). The primary analysis of AEs compared the frequency of events during the exercise session by randomization group. In a sensitivity analysis, all events occurring during the 12-week intervention period was planned. In both analyses, only the first event per individual was counted (for each type of adverse event).

Statistical analysis

We summarized baseline data using percentages, medians and inter-quartile rang (IQR), or mean ± standard deviation (SD). For secondary outcomes, we explored the effect of aerobic and resistance exercise on QoL and tests of physical performance using the absolute change in score at 12 weeks relative to baseline. To attain the efficiency of the factorial design, all participants who received the aerobic intervention (cycling and the combined group) were compared to all those who did not (resistance and control exercise group) and a similar approach was used for the resistance-training group. Analysis of covariance (ANCOVA) was used to adjust for the baseline score and the other intervention (main effect term).[26] To correct for multiple comparisons in the combined exercise group, the Bonferroni procedure ($P<0.025$) was used. We also estimated the confidence interval for the interaction term for the main study's primary outcomes.[27] Analyses comparing the groups at follow-up were conducted on an intention to treat basis. Missing outcome data was imputed using a last-value carried forward approach. Data analyses were performed using Stata Statistical Software, version 13 MP software (www.stata.com).

RESULTS

This trial is reported according to the CONSORT guidelines [28] and the recommendations for good practice for the design and analysis of pilot studies.[29]

Participant flow

Of the 100 patients screened for eligibility, 36 did not meet inclusion criteria and 33 declined to participate (Figure 1). The most common reason for exclusion was inability to provide consent (n=8) and the most common reason for declining participation was 'no interest in exercising during dialysis' (n=11). Thirty-one participants were randomized and 26 completed the study: (cycling, n=7); (resistance training, n=6); (combined cycling and resistance training, n=7); (stretching n=6). Complete outcome data were available for 27 participants.

RCT participants were predominantly male (77%), Caucasian (61%), with a median age of 57.6 years (IQR 49.2-75.1). The primary cause of ESRD was glomerulonephritis (32.3%) followed by diabetes (22.6%). Forty-eight percent of participants were diabetic, 90% had hypertension, and 26% had coronary artery disease, and 45% of trial participants were taking a beta-blocker. Overall, baseline physical functioning was low (mean PCS score of 35±8) and 39% of trial participants reported that they never exercised during their leisure time. Twenty-five of the 31 RCT participants participated in interviews (2 declined, 1 had a language barrier, and 3 changed location or dialysis modality).

The median age of patient interview participants was 57.5 years (interquartile range, [IQR] 49.2, 68.0); participants were primarily male (76%) and Caucasian (64%). Seven dialysis unit staff participated in pre-trial interviews (2 LPNs, 2 RNs, 2 service workers, and 1 technician); 86% were female. During the trial, 11 dialysis unit staff were interviewed (2 LPNs, 8 RNs, and 1 technician); 91% were female. Two dialysis unit staff participated in both sets of interviews.

Feasibility

Feasibility outcomes are shown in table 2. To highlight key themes regarding the trial's feasibility, exemplar quotes from the interviews of staff members and patients are shown in Tables 3,4, 6, and 7.

Dialysis unit staff (pre-trial interviews): barriers to implementation and in servicing

Although none of the staff members who were interviewed had received any prior formal education on IDE, most staff were not interested in attending an educational session. The preferred means of obtaining more information on IDE were by reviewing "*scientific data*" in their own time. Several staff preferred a practical approach to in servicing and suggested that we focus on teaching them how to set up the exercise equipment and complete study documentation (Table 3).

All staff members described potential benefits of IDE, such as improved dialysis and leg cramps, weight loss, increased confidence, and patients "*keeping busy*." However, it was common for staff to express concern that for many patients in the unit, IDE would be unsafe or would interfere with aspects of the dialysis treatment (Table 3). Several staff also expressed concern that the exercise equipment would have a negative impact on their workspace.

Dialysis unit staff (pre-trial interviews): selection of suitable candidates

Several staff emphasized the importance of selecting appropriate patients for IDE, typically referring to those patients who were stable during HD or younger. Several staff members requested that prior to enrolling a patient, we discuss the patient's suitability for the trial with them. (Table 3)

Patients' decision to participate in IDE

Several staff stated that patients' social networks in the unit were an effective means of disseminating information. Another staff member stated that after being approached for study participation, patients commonly elicited their opinion (Table 3).

Based on the data from the pre-trial interviews, modifications were made to the study protocol (Box 1).

RCT participants: recruitment

We exceeded the target accrual of 28 subjects over 12 weeks. Randomization to exercise intervention was not a barrier to participation. Patient interview participants reported that recruitment posters displayed outside of the unit and hearing other participants discuss their participation in the trial were effective means of promoting interest and participation in the study (Table 4).

Dialysis unit staff (mid-trial interviews): fidelity to the protocol

Although the physical demand of delivering the exercise equipment to patients was not described as onerous, data collection for the trial was. One staff stated that there were occasions when trial documentation "*didn't get done*." Several staff reported that there were technical challenges with retrieving HR and BP data for DCFs from the HD machines. Some staff also mentioned that recording the vital signs was too time consuming.

One commonly discussed barrier to the staff's involvement in the trial was not having enough staff and there being "no time"[20] to participate. Unit staff frequently made reference to the study as *"just one more thing"* and trial resource material was not frequently accessed. One staff member stated that the high workload on the unit negatively influenced their willingness to

participate. Although some staff members felt prepared to assist with the trial, several staff suggested that a lack of clarity on trial processes was a barrier to their involvement (Table 5).

RCT participants: fidelity to the protocol

The dropout rate over the study period was lower than our pre-specified threshold at 16%. Irrespective of exercise group allocation, patients' willingness to participate in IDE and their adherence to the exercise prescription was high: of the 1,038 training sessions offered, 87% of sessions were initiated (89% in the cycling group, 83% in the weights group, 90% in the combined group, and 86% in the stretching group). The exercises were performed as per protocol within all four groups for > 80% of exercise sessions (Table 2). Exercise parameters are shown in Table 6. For the active intervention groups, the mean RPE was within the targeted range and blood pressure and heart rate followed a similar trend: increasing during exercise and returning toward baseline post exercise. For the attention control, HR and BP were unchanged over the exercise period.

Although the exercises were protocolized, many participants viewed the intervention as tailored to their level (Table 5). Individualized instruction, progression based on RPE, and support from the kinesiologist[20] were commonly mentioned as strengths to the exercise program. For several patients, knowing there was the expectation of having to exercise facilitated adherence (Table 5).

Of the 1,038 exercise sessions that were offered, only three were terminated early. In all exercise groups, the most common reason for not initiating a given session was a physical complaint (7.5% of all prescribed sessions), commonly fatigue or feeling generally unwell. HD-related issues accounted for only 1% of non-initiated sessions, primarily due to central venous catheter dysfunction. Interestingly, in the post-trial participation interviews, many patients mentioned that

consistently obtaining exercise equipment from dialysis unit staff was the main barrier to exercise participation.[20] This reason for non-participation was not captured with the exercise DCFs. Only 1.5% of DCFs had missing data for reason not initiated.

Dialysis unit staff (mid-trial interviews): impact of the intervention

Overall, dialysis unit staff agreed that the exercise program was valuable for patients (Table 7). Their perception of benefit was based on patient report, as the trial results were not known at the time of their interviews. Staff viewed patients' subjective improvements, such as 'feeling healthier' as valid evidence of the benefits of IDE (Table 7). Many staff expressed that it was more feasible for them to participate in the trial once the main dialysis–related tasks were complete (typically after the first hour of the HD shift).[20]

RCT participants: impact of the intervention

Across all exercise groups, the patients' response to exercise was highly favorable (Table 7); 92% of participants reported they wanted to continue IDE after the trial and 63% wanted to continue exercising with their current regimen (Table 2). There were no crossovers during the trial and no change in the amount of physical activity performed outside of HD time was detected. Concealment of stretching as an active treatment was successful among patients and staff. One participant in the attention control withdrew from the study because he did not find stretching beneficial, "*it wasn't straining, it was just too easy*." Although another participant stated that stretching was "*boring,*" most participants in the control group viewed stretching as an important aspect of an exercise regimen (Table 7). One participant commented that their exercise routine was shorter than the other groups resulting in relatively less interaction time with the kinesiologist.

Patients commonly discussed the benefits of IDE and for many, these results motivated them to continue exercising (Table 7). Patients discussed the exercise-related benefits of IDE, such as greater strength and endurance. Several patients attributed improvements in daily functioning to participation in IDE. Improvements in dialysis-related symptoms were also mentioned, primarily decreased cramping and restless legs. The most frequently discussed benefit of IDE was that it *"helped kill the four hours"* and that it made the time on dialysis more enjoyable. For one participant, IDE served as "*an escape from the humdrum*."

Secondary outcomes

The absolute differences in scores for secondary outcomes are shown in Table 8. Scores are presented as crude mean differences and main effects. No significant differences from baseline to 12 weeks were found in the PCS or MCS components of the SF-36 or physical performance tests (6MWT, 30 second STS, 1 RM). For the SPPB, the absolute difference in score and (95% CI) were 1.7 (0.2, 3.3) for the main effect of cycling versus no cycling and 1.6 (0.05, 3.2) for weights versus no weights. This result is consistent with a minimal clinically important difference (values from 0.5 to 1.3 have been recommended).[22,30] Interaction terms for the planned primary outcomes of interest for the main study were: PCS -4.2 (-16.1, 7.6); P=0.47 and SPPB -2.9 (-5.5, -.38); P=0.026.

No serious adverse events were reported during the exercise sessions. Due to the low frequency of events in the trial overall, comparative statistics were not performed. Adverse events occurring during exercise are shown in Figure 2. Two patients in the combined group had AEs (one dialysis access complication, one episode of hypertensive urgency and one episode of hypotension). Two patients in the cycling group had AEs (two episodes of hypertension and ankle abrasions from the bike). In the weights group, there was one episode of access

complication. There were no AEs during exercise in the stretching group. The overall frequency of AEs was low (Figure 3). Notably, there were two episodes of hypotension in the control group, three in the cycling group, and one episode in the weights and combined exercise group.

Discussion

The purpose of this pilot study was to evaluate the feasibility of an IDE exercise intervention and to perform an exploratory analysis of cycling and weight training each compared with control on QoL, tests of physical performance, and strength. We demonstrated feasibility of recruitment and high patient acceptability. In addition, few exercise trails in this population have attempted to blind participants to group allocation.[4] We demonstrated a low risk of contamination and attrition with the use of an attention control and blinding to study hypothesis. However, primarily based on the findings from the interviews with dialysis unit staff and trial participants, several modifications to the study protocol are required prior to proceeding with the main study.

Readiness for change is considered critical to the successful implementation of complex interventions in healthcare settings.[31] In this pilot, we found that there was a lack of readiness among dialysis unit staff for IDE. Several of the factors that influenced unit staff's preparation, motivation, and ability to participate in this trial have been cited in other studies as barriers to IDE and clinical program implementation: lack of time,[32,33] high patient care demands,[34] and safety concerns with the exercise equipment in their workspace [32]. In our previous study, we also identified a lack of support from management and personal beliefs about exercise as influencing staff readiness for IDE.[20] Therefore, prior to recruitment for the main study, it will be necessary to develop a strategy for understanding staff readiness at potential study sites. Although the influence of education on staff participation in IDE remains unknown, in one study, patient and staff thought that a better understanding of IDE would have improved their initial

participation.[34] In this pilot, the lack of interest among many unit staff for IDE education was a barrier to engaging staff. Other more convenient forms of delivering education i.e. videos online and reading material on the unit were not highly accessed. Given that for unit staff in this study seeing and hearing the benefits from their patients first-hand positively influenced their perceptions of the intervention, a pre-trial demonstration phase may be the most effective means of promoting acceptability of IDE. Despite the concerns expressed in the pre-trial interviews about patient and workspace safety, that no unit staff mentioned these concerns in the second set of interviews (once the intervention was established), also supports the value of providing staff with the opportunity to experience IDE in their own setting prior to study start.

In addition to requiring the unit staff's assistance with IDE delivery for practical reasons, we identified other reasons why their participation was important. First, due to their frequent and prolonged contact with patients, dialysis unit staff are in a unique position to assist patients with decision-making.[35] As we found that some patients seek the opinion of dialysis unit staff on study participation, it is important that those who engage in these discussions are prepared to discuss the risks and benefits of IDE with patients. Although 30% non-participation is comparable to other trials in this population,[15,17,18,36] it is possible that the staff's perceptions of IDE influenced patients' decision to participate. Second, and as described in our qualitative study, the patients' perspective that unit staff's assistance and encouragement with IDE was consistent with their role as carer and patient advocate has the potential to influence patient acceptability of IDE.[20] Many patients experienced difficulty consistently obtaining exercise equipment from unit staff, which has clear implications for patient adherence.[20]

For unit staff, exercise data collection was too time consuming and resulted in missing data. This issue was recognized early in the trial and resolved with greater involvement from study staff.

This strategy is not feasible for a multisite study and exercise vital signs will be limited to pre-, mid-, and post-exercise. We also found that for unit staff, feasibility of workflow integration was affected by the timing of when in the dialysis treatment that IDE was performed.[20] To decrease the risk of hypotension, other trials have typically completed exercise within the first one to two hours of the HD session [15,37,38] and starting exercise within the first hour of HD is often recommended. However, this is often the busiest time for unit staff and in settings where there are staffing constraints, and may be a barrier to optimal staff engagement. We are only aware of one trial where IDE was performed in the final two hours of the HD session and this was well-tolerated.[39] Our protocol specified that patients finish their exercise within the first 3 hours of the dialysis shift. The safety of this approach is supported by our blood pressure and safety data. A more detailed evaluation of the timing of the HD session and its effect on blood pressure would provide important insight into how to optimize both the safety and the practicality of IDE delivery.

Most studies evaluating exercise adherence in people with kidney disease have focused on individual determinants and not evaluated program factors.[40,41] In this study, progression based on RPE and individualized instruction facilitated acceptability among patients. As described in our qualitative study, patients perceived the kinesiologist's technical support as conveying a sense of esteem and capability.[20] This interaction may have served to increase participation, irrespective of group assignment. In addition, the most commonly mentioned benefit to IDE was that it helped pass the time, suggesting that many patients are interested in participating in interventions where they can use their time on HD more constructively. It also suggests that some of the perceived improvement in wellbeing could be mediated through engagement in an activity, rather than exercise. These findings underscore the importance of continuing to use a supervised attention control for the main study. However, given the potential

impact of the interaction with the exercise specialist on intervention acceptability, it will be important to ensure the time spent with the kinesiologist is equal across groups.

We did not detect differences in physical activity or exercise performed outside of the unit during the trial, nor was the trial powered for this outcome. The primary aim of this pilot study was to evaluate feasibility and small sample sizes were used. Based on 80% power to detect a difference of 5 points[42] in the PCS score in the main effect of aerobic and the main effect of resistance, 32 participants per arm are required. Allowing for 25% dropout per arm, the main study will enroll 160 patients. The antagonistic interaction term for the SPPB will also need to be explored in more detail, as this could be a spurious finding due to multiple outcome testing.

Conclusions

To our knowledge, this is the first feasibility study to use qualitative methods to evaluate IDE implementation within an RCT design and to address known limitations to trial design. In addition to informing the design of our future definitive study, these results are useful in the development of future trials and for guiding clinicians with the implementation of their own IDE interventions. The key lesson learned was that within this protocolized setting, the potential for unit staff readiness to influence aspects of feasibility, such as recruitment and patient adherence was high. Therefore, prior to study start, more time will need to be invested in understanding and enhancing staff readiness. For engaging unit staff, a less didactic approach that is also integrated into their existing workflow may be highly effective.

Authors' contributions

Authorship followed ICMJE guidelines. ST was responsible for the inception and design of the project and prepared the manuscript. MH, SK, AM, and MT participated in the design of the study and provided methodological input. IG participated in the design of the exercise intervention. AL provided statistical support. All authors read and approved the manuscript.

List of abbreviations

End-stage renal disease (ESRD); rating of perceived exertion (RPE); Intradialytic exercise (IDE); Hemodialysis (HD); Quality of life (QoL); Randomized controlled trial (RCT); Data collection form (DCF); Adverse event (AE); PCS (physical component score); MCS (mental component score); SPPB (short physical performance battery); 6MWT (6-minute walk test); STS 30 seconds (30-second sit-to-stand); 1-RM (one repetition maximum): Heart rate (HR); Blood pressure (BP); inter-quartile range (IQR); standard deviation (SD).

Competing interests

The authors have no competing interests to declare.

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Data Sharing

No additional data are available

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Figure 1: RCT participant flow

Table 1: Baseline characteristics of trial participants

	All (n=31)	Cycling (n=8)	Weights (n=7)	Combined (n=8)	Stretching (n=8)
Age[1]	57.6 (49.2-75.1)	66.9 (55.8-82.4)	59.7 (45.9-81.4)	60.3 (54.7-68.4)	49.3 (43.0-62.3)
Sex (male)	24 (77)	8 (100)	6 (86)	3 (38)	7 (88)
Time on HD (yrs)	3.2 (1.7-4.4)	3.7 (2.4-4.6)	2.8 (2.0-4.0)	2.9 (0.7-2.3)	3.3 (1.2-6.2)
Ethnicity					
Caucasian	19 (61)	7 (88)	3 (43)	5 (63)	4 (50)
Southeast Asian	4 (13)	1 (13)	1 (14)	1 (13)	2 (25)
Aboriginal	3 (10)	0	2 (29)	0	1 (13)
Other	5 (16)	0	1 (14)	2 (25)	1 (13)
Cause of ESRD					
Diabetes	7 (22.6)	2 (25)	1 (14.3)	2 (25)	2 (25)
Glomerulonephritis	10 (32.3)	1 (12.5)	5 (71.4)	4 (50)	0
Hypertension	1 (3.2)	1 (12.5)	0	0	0
Polycystic kidney disease	3 (9.7)	1 (12.5)	0	1 (12.5)	1 (12.5)
Reflux/urological	3 (9.7)	1 (12.5)	0	0	2 (25)
Other	5 (16.1)	2 (25)	1 (14.3)	0	2 (25)
Unknown	2 (6.5)	0	0	1 (12.5)	1 (12.5)
BMI	24.7 (21.6-29.9)	23.6 (22.2-25.7)	25.9 (24.6-29.9)	25.3 (20.0-30.8)	24.2 (20.4-33.8)
Diabetes	15 (48)	3 (38)	3 (43)	5 (63)	4 (50)
Hypertension	28 (90)	8 (100)	7 (100)	7 (88)	6 (75)
Beta blocker	14 (45)	4 (50)	4 (57)	3 (38)	3 (38)
Coronary artery disease	8 (26)	4 (50)	1 (14)	2 (25)	1 (13)
Heart failure	7 (23)	4 (50)	3 (43)	0	0
QoL-PCS	35 ± 8	35 ± 9	32 ± 9	35 ± 10	36 ± 3
Never exercise in leisure time	12 (39)	3 (38)	4 (57)	1 (13)	4 (50)

1. Median (IQR interval); N with (%) or mean (± standard deviation); totals do not always add to 100 due to rounding

Table 2: A priori feasibility criteria and outcomes

Feasibility criteria	Feasibility outcome
Recruitment	
Accrual: 28 participants over 12 weeks	31 participants over 12 weeks
Reason for non-participation: proportion of screened patients unwilling to be randomized must be ≤ 20%	No patients reported randomization to exercise type as a reason for non-participation.
Fidelity to the protocol	
Drop-out: ≤ 25% of study participants withdrawing participation	**16% of participants dropped out:** Cycling n=1, transplanted Resistance n=1, injury from motor vehicle collision Combined n=1, moved dialysis unit Attention control n=2, nausea and vomiting; did not like exercise
Adherence (willingness of participants to participate): of all exercise sessions offered,[1] ≥ 70% were initiated	**87% of prescribed exercise sessions were initiated:** Cycling 89% Weights 83% Combined 90% Attention control 86%
Adherence (accordance with the exercise prescription): of all exercise sessions offered, ≥ 70% were performed at the prescribed time/volume and intensity	**86% of prescribed exercise sessions were performed as prescribed:** Cycling 87% Weights 84% Combined 88% Attention control 86%
Impact of the intervention	
Acceptability of the exercises: overall ≥50% of participants reporting that they would like to continue their current intradialytic exercise program after the study is over	**63% of participants said they would continue with their current exercise** Cycling 50% Weights 50% Combined 100% Stretching 38%
Change in the amount of physical activity performed overall: difference in the HAP scores between baseline and 12 weeks[2]	MAS: Cycling versus no cycling 4.3 (-2.8, 11.5) P=0.3 Weights versus no weights -1.2 (-8.4, 6.0) P=0.7 AAS: Cycling versus no cycling 1.1 (-7.7, 9.9) P=0.8 Weights versus no weights -0.9 (-9.7, 7.8) P=0.7

Difference in the proportion of participants who reported never exercising outside of HD time	Baseline: 39% of participants exercised almost never or never exercising versus 12 weeks: 29% of participants exercised almost never or never (P= 0.55)
Contamination: any participant who adopted the exercise(s) of another intervention group during the study period	No participants from the cycling, weights, or stretching groups reported performing the other group's exercise
ɔntamination: any participant who adopted the ercise(s) of another intervention group during the ıdy period	ɔ participants from the cycling, weights, or stretching ɔups reported performing the other group's exercise

HAP (Human Activity Profile); MAS (maximal activity score); AAS (adjusted activity score).

1. Offered sessions exclude sessions lost to study dropout. 2. Analysis performed for main effects adjusting for the baseline score and other factor.

Table 3: Quotes from pre-trial interviews with dialysis unit staff

Barriers to implementation and in servicing
In servicing *"I would prefer to read, it's easier. And to have it always in my pocket--a reference."* *"As long as we know what—where the documentation's required; I don't think anything else to be honest with you"* ***Patient safety and staff workflow*** *"The other thing you're going to have is once the patients start moving about, if they've got their fistula access, it is going to be compromised, and I would not compromise that."* *"They could slip out of their chair; they're not sitting properly, they could split their shin with it because they're diabetic, that could cause problems for them…"* *"And we are very, very busy, [at changeover] and nothing's supposed to be around us because we're running from machine to machine to get ready for the next patient."*
Selection of suitable candidates
"Some young people [would be good for IDE] …But I cannot say how many. *"I think just being very careful who you pick for the study. It has to be somebody who's physically able to do it, mentally competent. Some people might seem like they're physically able, but they're not mentally able."* *" Actually, [pause] just asking for input on patients to make sure that they are suitable...Or even before you ask them, make sure they are suitable for that program [IDE}. Because I mean, there's a lot of patients they aren't stable and their blood pressure will drop..."*
Patients' decision to participate in IDE
"So I think because a lot of them are friends here, so they talk, and, you know, if you're doing that, "What do you think about it?" So they ask each other. Or they can even do it together if they're sitting side-by-side; you know, "Oh, that's kind of fun."... 'Cause a lot of things happen that way here, 'cause they listen to what other patients talk to nurses about, then they think, "Oh, okay, I'll try that, too." *"After the conversation with research person, they usually ask our opinion."*

Box 1: Modifications to the study protocol following pre-trial interviews with unit staff

Trial protocol item	Initial plan/barrier	Modification
In-servicing format	Didactic sessions on the benefits of exercise in people with ESRD and one practical session with the exercise equipment	Two practical in-services on study procedures and equipment set-up Video posted on YouTube on the exercises and how to assist patients with equipment set-up Education materials (articles, pamphlets, summaries) on IDE placed on the unit for staff
Workspace safety for staff	Exercise equipment as workspace hazard	Unit staff identified where equipment would be stored on the unit With unit staff input, protocols for equipment set-up and removal were written into study protocol
Recruitment	Only study staff selects suitable candidates	Prior to enrolling a patient, the charge nurse was consulted regarding any dialysis-related safety concerns
Implementation	Include several unit staff members as volunteer "exercise champions" to lead unit staff and liaise with study staff	No volunteers found. Identified four staff "point people" who were already in leadership roles in the unit to informally check in with study staff on trial implementation

Table 4: Exemplar quotes from RCT participants on trial recruitment

Patients' decision to participate in IDE
"No, hadn't thought about—well, I saw the posters and thought, "Hm, interesting. Maybe… I hadn't figured you could do anything...[on dialysis]."
"First of all, it was a novelty, and then it was interesting to see how it was a wave of interest; it was a domino effect. And there was a real nice buzz... The [other] patients were, "Hey, you're doing—what are you doing?" etc., etc., so that was super.

Table 5: Exemplar quotes from interview participants on fidelity to the protocol

Dialysis unit staff (mid-trial interviews)
"...we check patients every half-hour for their blood pressures and all the dialysis machine readings and stuff like that, so I find also recording the blood pressure is very time-consuming, because we can go back and look at the list of blood pressures on their machine after, but then we just go back and find them or you have to be recording them every 5 or so minutes, so you're running back and forth between doing your other work and so forth. So I find it's very busy in that respect." *"It was just difficult to add something for us to do, 'cause initially, I think what the thought was to teach all the nurses what the patients were supposed to be doing, but it was just difficult to in-service everybody. They were, like, "Okay, so this is how you fill out the sheet"—'cause the sheet, to me, I'm so confused working with it. And sometimes—oftentimes, we're short-staffed, so we don't have the staffing to even get this equipment and all that kind of stuff. So it ended up being they just ended up coming every run and doing the exercise study with the patients. ... I think there was a lot of resistance from staff to really help out with it."* *"I am prepared because they also have an in-service, and they also have [the kinesiologist] here to show us, she also give us e-mail and show with the video, show us how the exercise going. But I be honest, we don't have time to look at that. We don't have time to sit down and look at that video!"*
RCT participants (post-trial participation)
"Yes, because I was starting from zero exercise, so I wasn't sure how much, how hard it would get, how—if I could keep up to what they wanted, that kind of thing...But they did it very gradual, and [the kinesiologist] was very good about telling us ahead of time when they're going to put up the weights or when they're going to increase the minutes of pedaling, so you knew what to expect." *"Well, we were increased at our own pace, which I really liked, because I just went at my own level."* *"Also I want to tell you that I have a treadmill at home, but sometimes I do it, sometimes I don't. But here, it's, like, we have to..."*

Table 6: Exercise parameters for the four exercise groups

	Cycling	Weights	Combined	Stretching/control
Borg (Intensity, RPE)	13 ± 1	13 ± 1	13 ± 1	8 ± 2
Mean amount of exercise performed	28.0 ± 3.4 minutes	36 ±12 (repetitions) 5.0 ± 3.4 (lbs)	27.5 ± 8.8 minutes; 35 ± 12 (repetitions) 3.7 ± 1.8 (lbs)	NAP
Systolic BP (mmHg)	Pre: 136 ± 20 During: 150 ± 26 Post: 130 ± 21	Pre: 123 ± 26 During: 127 ± 27 Post: 117 ± 26	Pre: 121 ± 28 During: 126 ± 24 Post: 116 ± 26	Pre: 119 ± 22 During: 119 ± 22 Post 118 ± 20
Diastolic BP (mmHg)	Pre: 74 ± 16 During: 80 ± 19 Post: 75 ± 16	Pre: 66 ± 15 During: 67 ± 16 Post: 63 ± 15	Pre: 62 ± 13 During: 67 ± 13 Post: 63 ± 13	Pre: 70 ± 14 During 70 ± 15 Post 69 ± 14
Heart rate (bpm)	Pre: 66 ± 14 During: 85 ± 20 Post 77 ± 17	Pre: 71 ± 12 During: 78 ± 13 Post: 74 ± 13	Pre: 69 ± 11 During: 79 ± 13 Post: 73 ± 11	Pre: 78 ± 17 During: 77 ± 16 Post: 77 ± 17

RPE (rating of perceived exertion); BP (blood pressure); HR (heart rate); bpm (beats per minute); lbs (pounds).

Pre, post, and during exercise BP and HRs are a means ± SD for initiated exercise sessions.

Table 7: Exemplar quotes from interview participants on the impact of the intervention

Dialysis unit staff (mid-trial interviews)
The benefits of IDE *"A lot of them—well, I think probably all of them increased their muscle mass and they have more strength at the end of the program, so they were quite pleased."* *"So yeah, the patients, I find, like the ones on the study feel good about themselves. They feel good, and I think they feel better…"*
RCT participants
Acceptability of the exercises *"I thought it was—everything was set up perfectly for me. I could do each exercise. Of course, it's a little cumbersome doing a few of the leg reps in a chair, but it's not insurmountable, by far."* "*Well, because all I had to do was the stretches, in a way, it was kind of boring, I think. But it's not like stretches aren't good for you; I mean, it is, they're good for you. But I don't know, it's just—it was alright; I wouldn't say it was all that exciting or anything."* *"…I was quite amazed that even with the stretchy bands—and it's a good thing I started with those to kind of loosen me up a little, because I was—like, I had muscles that were sore..."* ***The benefits of IDE*** *"I'm more steady on my feet. My legs were pretty shaky before, and now they're not."* *"..even my wife has noticed I've got more muscle tone on my legs. And I was really surprised about that, 'cause I didn't think dialysis patients could—and especially even at my age get that kind of deal. But I even noticed myself, I do have more muscle tone."* *"…Like, I do a fair amount of walking, myself, probably 12 blocks a day, and so my legs were fairly good, but I cannot keep up to my wife if we went shopping. Now I can."* *"Oh, I get cramps. Every dialysis run, I had cramps, but after doing exercise, I—no more cramps now."* *"I had restless leg, and I still have it, but surprisingly, not as drastic..."*

Table 8: Secondary outcomes (QoL, tests of physical performance, and strength)

Outcome	Cycling (n=8)	Weights (n=7)	Combined (n=8)	Stretching/control (n=8)
PCS; mean difference & SD	5.2 ± 9.3	4.1 ± 8.0	1.7 ± 7.4	3.4 ± 7.3
Main effects (95% CI)	Cycling vs no cycling -0.076 (-5.9, 5.8); P=0.979		Weights vs no weights -1.82 (-7.7, 4.1); P=0.53	
MCS; mean difference & SD	-2.3 ± 10.7	-3.4 ± 9.1	-1.5 ± 5.9	0.70 ± 7.5
Main effects (95% CI)	Cycling vs no cycling 0.23 (-6.0, 6.5); P=0.94		Weights vs no weights 0.21 (-6.5, 6.9); P=0.95	
SPPB; mean difference & SD	1.9 ± 2.4	1.4 ± 1.9	1.0 ± 1.2	0.63 ± 1.2
Main effects (95% CI)[1]	Cycling vs no cycling 1.7 (0.2, 3.3) P=0.028		Weights vs no weights 1.6 (0.05, 3.2) P=0.044	
6MWT; mean difference & SD	42.3 ± 88.8	54.9 ± 52.9	39.0 ± 76.8	0.8 ± 44.0
Main effects (95% CI)	Cycling vs no cycling 12.8 (-36.1, 61.6) P=0.60		Weights vs no weights 30.7 (-17.8, 79.2) P=0.21	
STS 30 seconds; mean difference & SD	0.9 ± 2.2	1.6 ± 2.7	1.4 ± 3.5	1.4 ± 4.3
Main effects (95% CI)	Cycling vs no cycling -0.31 (-2.7, 2.1) P=0.79		Weights vs no weights 0.42 (-2.0, 2.8) P=0.73	
1-RM; mean difference & SD	11.6 ± 10.7	8.9 ± 5.5	4.9 ± 11.6	9.3 ± 10.1
Main effects (95% CI)	Cycling vs no cycling -3.4 (-11.0, 4.2) P=0.37		Weights vs no weights -2.8 (-9.9, 4.2) P=0.42	

PCS (physical component score); MCS (mental component score); SPPB (short physical performance battery); 6MWT (6-minute walk test); STS 30 seconds (30-second sit-to-stand); 1-RM (one repetition maximum)

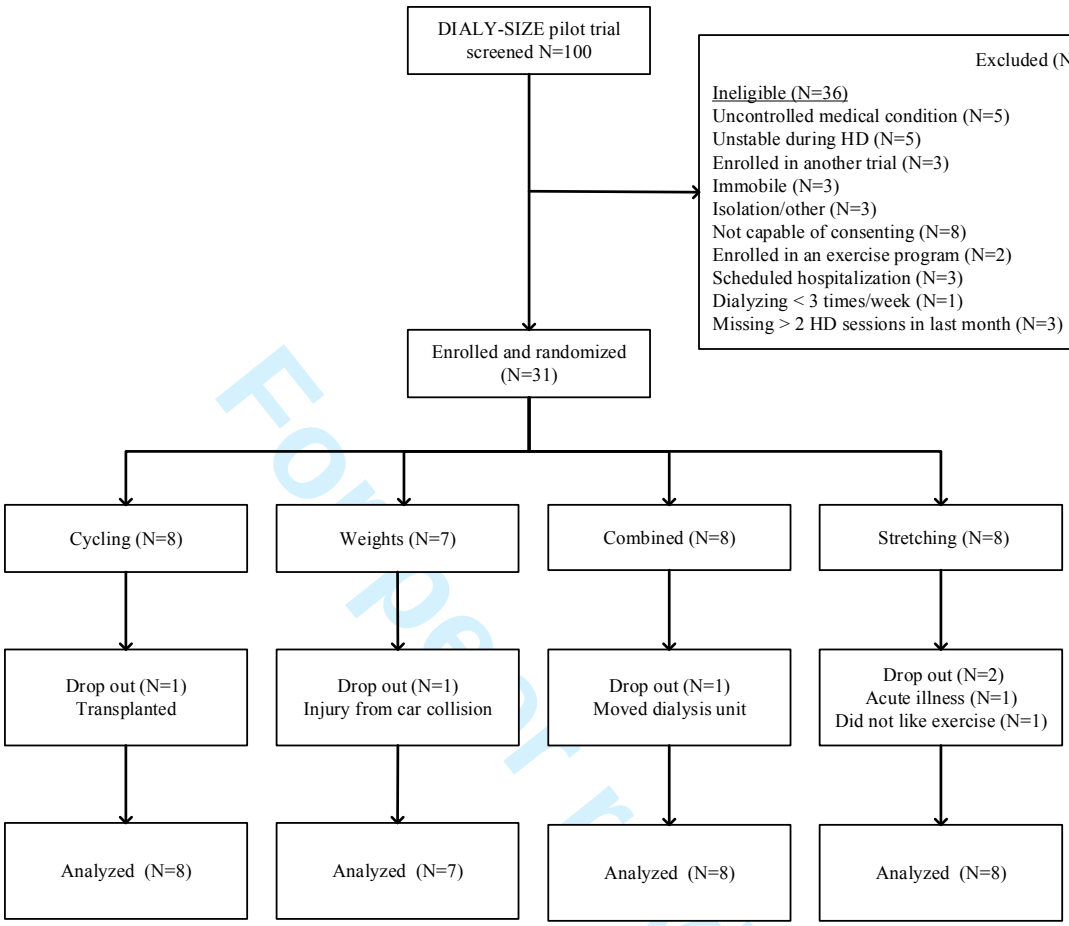
Models are adjusted for baseline score and the other main effect term. 1. Interaction term included in the model (P=0.026)

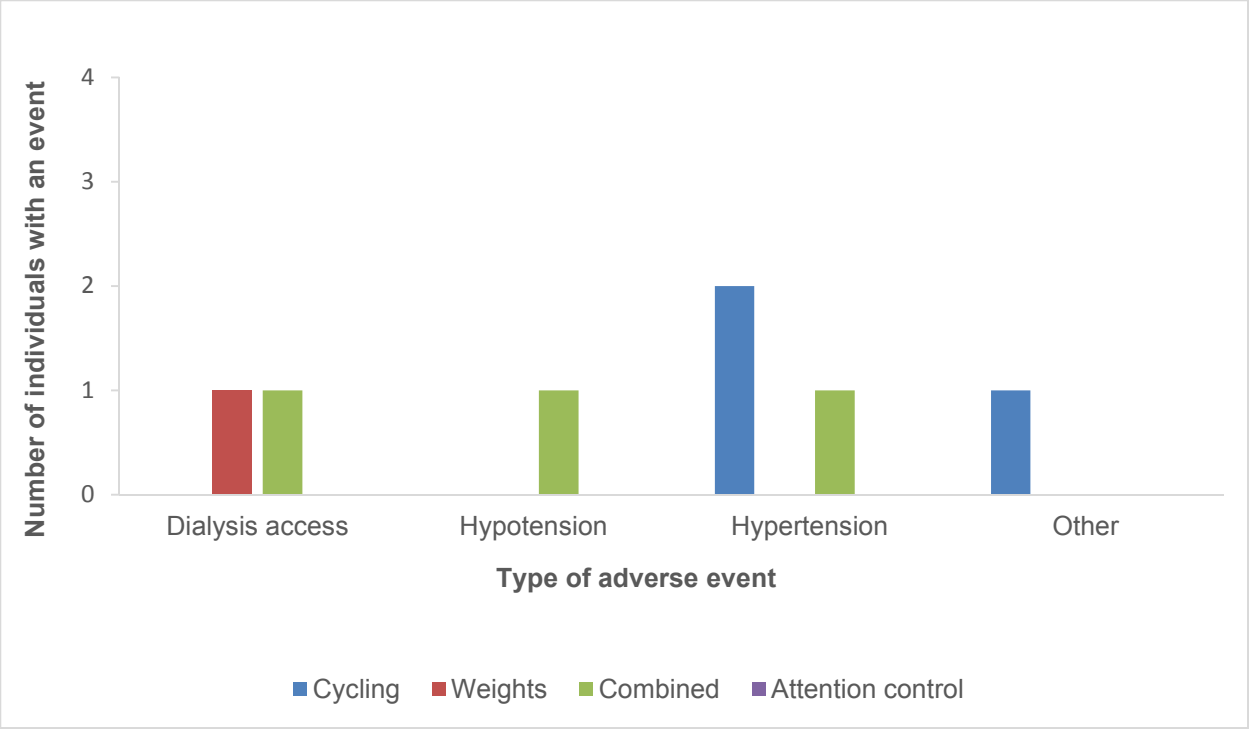
Figure 2: Adverse events occurring during the exercise session

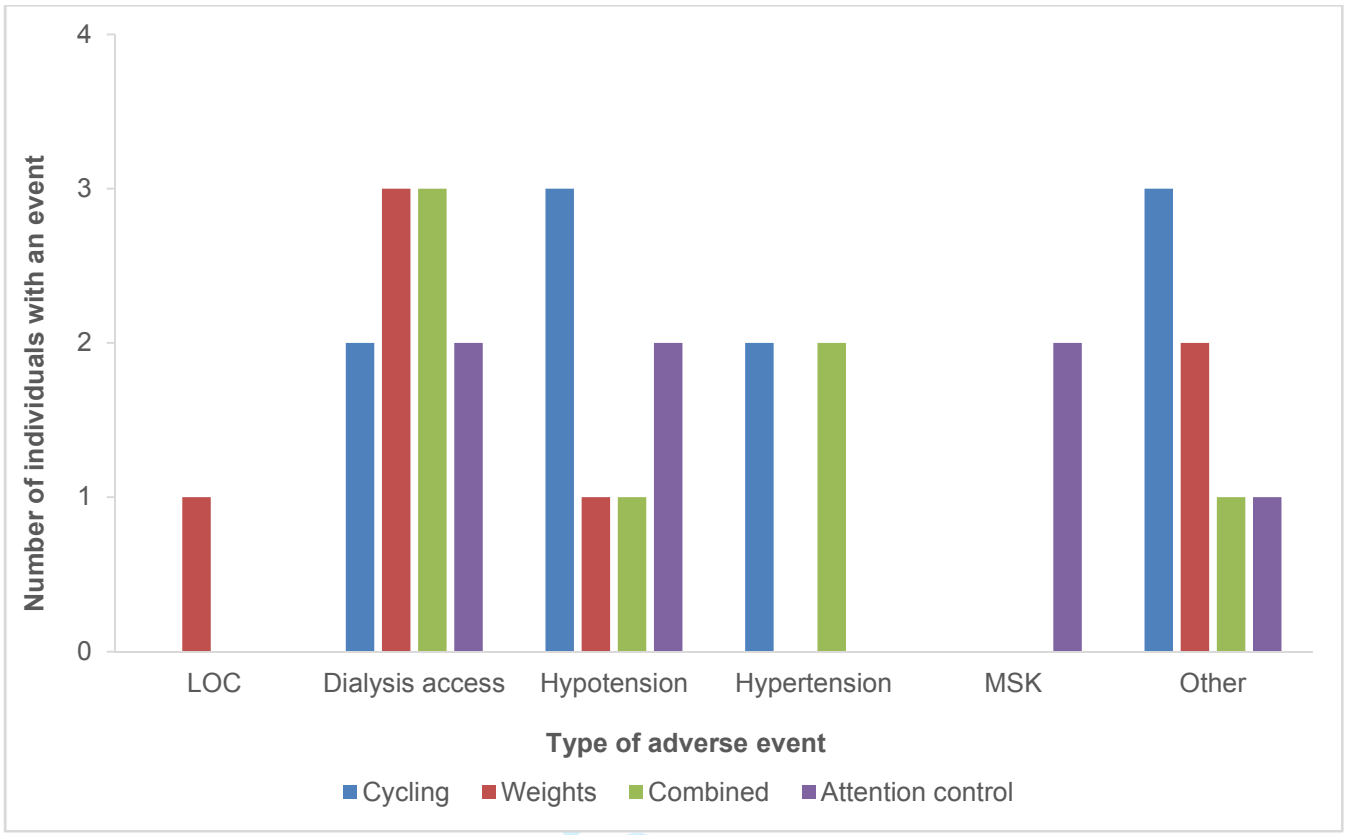
Dialysis access complications= re-needling, hematoma

Figure 3: Adverse events occurring over the study period

Dialysis access complications= re-needling, hematoma







CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Title page
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NAP
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NAP
Sample size	7a	How sample size was determined	22
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NAP
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
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	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NAP
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NAP
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13 (and figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	13 (and figure 1)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	No
	14b	Why the trial ended or was stopped	NAP
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 13 and Table 8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 18-19 & table 8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NAP
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NAP
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Page 19 & Fig 2 &3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 22-23 & 4
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Page 20-22
Other information			
Registration	23	Registration number and name of trial registry	Page 3
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 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.

NAP=not applicable
NA=not available

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A randomized factorial mixed-method pilot study of aerobic and resistance exercise in hemodialysis patients: DIALY-SIZE!

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A randomized factorial mixed-method pilot study of aerobic and resistance exercise in hemodialysis patients: *DIALY-SIZE*!

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Objectives

For people with end-stage renal disease requiring hemodialysis exercise can improve aspects of quality of life (QoL). However, the relative benefits and risks of different types of exercise in this population is unknown. Therefore, this pilot study aimed to evaluate the feasibility of a main study evaluating the efficacy of cycling and resistance exercise each performed during the hemodialysis treatment on QoL.

Methods

In this factorial (2 x 2) pilot trial, 31 hemodialysis patients were randomized to cycling, resistance, cycling and resistance, or an attention control. Feasibility was defined a priori by criteria on recruitment, fidelity to the protocol, and patient response to the intervention. To better understand feasibility, we conducted interviews with dialysis unit staff and trial participants. As secondary outcomes, we estimated the main effect of cycling and weights each compared with control on QoL, physical function, and strength.

Findings

We exceeded the target accrual of 28 subjects over 12 weeks. Irrespective of exercise group allocation, adherence was high: of the 1,038 training sessions offered, 87% were initiated, and over 80% of exercise sessions were performed as per protocol. Progression based on perceived exertion, individual instruction, and interactions with the kinesiologist facilitated acceptability across exercise groups. Using an attention control, measures of contamination and attrition were low. Important barriers to unit staff readiness for the intervention were initial safety and workflow concerns, unit workload, and onerous data collection. Secondary outcomes were not statistically significant. Adverse events were low and did not increase with a higher volume of exercise.

Conclusions

The main study is feasible with minor modifications. In addition to practical assistance, involvement from unit staff could increase patient participation and improve trial implementation. Strategies to increase acceptability of the intervention for staff include improving workflow integration and using a pre-study demonstration phase to introduce the intervention.

Trial registration: ClinicalTrials.gov NCT02234232

Strengths and limitations of this study

- To our knowledge, this work is the first to include qualitative methods in evaluating the design of an exercise trial in hemodialysis patients.
- Understanding patient and dialysis unit staff perspectives on trial processes and the intervention was critical in identify barriers to trial implementation and for purposing strategies to improve these.
- Detailed information on aspects of trial delivery contributes useful knowledge to the renal exercise literature on how key methodological and practical limitations could be feasibly improved in order to increase trial quality, relevance, and potentially effectiveness.
- Due to limited sample size, we could not triangulate patients' experiences of intervention factors by high or low adherence.
- Our focus was on identifying the factors that influenced trial implementation and how these factors would influence the longer-term sustainability of the intervention is not clear.

INTRODUCTION

While hemodialysis (HD) is a life-sustaining therapy for people with end-stage renal disease (ESRD), it is associated with low quality of life (QoL) [1,2] and a marked decline in functional status. [3] Although the benefits of exercise in this population have been recognized, few studies have evaluated how different types of exercise can influence QoL, and the majority of interventions have evaluated aerobic exercise.[4,5] How to most effectively engage patients in the optimal exercise prescription and achieve the desired outcome while minimizing risk, is critical to increasing patient participation.

Many generic QoL scales used in exercise studies in people with ESRD address the individual's perception of their ability to meet the demands of everyday living. However, performance of daily tasks is more dependent on musculoskeletal fitness than aerobic capacity.[6,7] In the elderly non-ESRD population,[6,8] and in people with congestive heart failure (CHF),[9] resistance training is a promising means of improving QoL and decreasing disability. However, whether resistance training confers specific benefits relevant to aspects of QoL in people with ESRD is not known.

The aim of our future multicenter study is to evaluate the effect of two types of exercise (cycling and resistance) each compared to control and performed during the HD treatment (intradialytic exercise, [IDE]) on QoL and physical performance using a randomized factorial design. Prior to proceeding with this main study, a pilot was warranted to evaluate the feasibility of the design. Although delivering exercise during HD has been associated with greater adherence compared to a home-based exercise program,[10] few pilot studies have rigorously evaluated the feasibility or the integrity of trial implementation and we are not aware of any studies that have included

qualitative methods to provide a more comprehensive understanding of the implementation process.[11]

METHODS

Study design

This mixed-methods, single-center, randomized, factorial (2 x 2) trial included qualitative interviews with trial participants and dialysis unit staff to evaluate domains of feasibility defined a priori: recruitment, fidelity to the study protocol, and the response of trial participants and dialysis unit staff to the intervention. In a secondary analysis, we explored differences in QoL, physical function, and strength. The two factors evaluated were aerobic exercise (cycling) and resistance exercise (leg weights). HD patients were randomized to one of four groups: cycling, leg weights, combined leg weights and cycling, or stretching (an attention control). The rationale for using a factorial design is for the efficiency of testing more than one intervention in the same participants.[12] (There is no known interaction between aerobic and resistance exercise in the literature i.e. the effect of aerobic exercise does not differ in the presence of resistance exercise). All exercises were performed during HD at each thrice-weekly dialysis session over 12 weeks (36 sessions). The Health Research Ethics Board at the University of Alberta approved this study. The study protocol was registered under NCT02234232.

Setting and participants

The trial setting was an outpatient dialysis unit in Edmonton, Canada that serves approximately 110 patients. A study coordinator recruited participants during their HD sessions. Inclusion criteria were: adult (age ≥18); dialysis dependent for ≥ 3 consecutive months; receiving ≥ 3 dialysis treatments per week; mobile (any distance, walking aid permitted); at least one non-prosthetic limb; and capable of providing consent. Exclusion criteria were: currently enrolled in a

clinical trial; missing an average of more than 2 dialysis sessions per month; planned move or modality change within the next 4 months; currently enrolled in a structured exercise program; scheduled hospitalization for > 1 week; unstable during HD; and any uncontrolled medical condition that would preclude participation in a low/moderate intensity exercise program.[13]

Randomization and blinding

Participants were randomized on a 1:1:1:1 ratio using a computerized randomization procedure with permuted blocks of eight and twelve. Allocation was concealed in serially numbered, opaque, sealed envelopes. The randomization list was generated by the statistician and kept in a locked cabinet. Given the open setting of the dialysis unit and the nature of the intervention, it was not logistically possible to blind the participants or the kinesiologist to treatment allocation. Therefore, participants and HD unit staff were blinded to the study hypothesis. Patients were informed that they would be randomized to one of four different exercise regimens; a stretching exercise group served as the attention control. Kinesiologists assessed all tests of physical performance; a blinded assessor performed outcome assessments at 12 weeks.

Exercise intervention

A kinesiologist instructed all participants on how to perform exercises and supervised a minimum of two of the participants' thrice-weekly exercise sessions. In addition, the kinesiologist supervised the first three exercise sessions and the first session following progression of the exercise prescription. When the kinesiologist was not present, dialysis unit staff assisted patients with equipment set-up and completed trial documentation. Throughout the study, unit staff were also asked to help motivate patients by providing verbal encouragement. The kinesiologist instructed all participants on how to use rating of perceived exertion (RPE) with the Borg scale (6-20).[14] The intensity of exercise for the aerobic, resistance, and

combined intervention groups was prescribed at a level of 12-14 or "somewhat hard" on the Borg (RPE) scale and a RPE level of 8-9 ("very light") for the stretching group.

Aerobic intervention

Each session included a five-minute warm-up and cool-down on the cycle ergometer at an RPE of 9-11. The cycling protocol started with 15 minutes of cycling with time increased by 2.5 minutes each week. The resistance was adjusted to maintain the target RPE. One of two types of cycle ergometers were used according to compatibility with the type of dialysis chair: the Monark 881E cycle (Health Care International, Langley, WA) or the TherapyTrainer (Interactive Motivation, Greely, CO).

Resistance intervention

Ankle weights (Fabrication Enterprises, White Plains, NY) were used for knee extension, knee flexion, and hip flexion. A Theraband (The Hygenic Corporation, Akron, OH) was used for hip abduction. Each session included a warm-up of one set of the four exercises against gravity. Based on RPE, exercises progressed from one set of 10-15 repetitions up to three sets. Weight or resistance was increased when the patient's RPE was less than target.

Combined intervention

Participants in the combined training group performed the full resistance exercise program followed by the complete cycling program.

Attention control

To equalize the effect of co-interventions,[15] the control group performed a non-progressive stretching routine during dialysis. Participants performed two sets each of four exercises: pelvic

tilts, gluteal stretch, calf, and hamstring stretch. A TheraBand Stretch Strap (The Hygenic Corporation, Akron, OH) was used for the calf and hamstring stretches.

Data collection

Clinical data were collected at baseline via interviews with participants and chart review. Survey data, questionnaires, and tests of physical performance were performed at baseline and at 12 weeks. At each session, the following data was recorded on exercise data collection forms (DCFs): pre- and post-exercise blood glucose (for diabetics), heart rate (HR), blood pressure (BP), reason for exercise non-participation and early termination, if applicable. During exercise, HR, BP, and RPE were documented every five minutes. Data on adverse events (AEs) were collected via interview at each exercise session with the kinesiologist and by chart review.

Primary outcomes

The primary outcome of feasibility was defined by a priori criteria (Table 1) and focused on the following: recruitment (rate of accrual, reason for non-participation); fidelity to the protocol (dropout, adherence); response to the intervention (physical activity level outside of the dialysis unit, adoption of the other group's exercise [contamination]), and acceptability of the intervention.

Recruitment

Previous intradialytic exercise trials report 20-46% of screened patients were randomized.[16–19] We estimated that approximately 85% of the 110 patients in this unit would be available for screening and targeted recruiting 28 subjects. Based on the assumption that interested patients may already have preferences concerning exercise that would make randomization undesirable, unwillingness to be randomized to exercise type was selected as a feasibility criterion. Reason for nonparticipation in the trial was based on self-report.

Fidelity to the protocol

Based on dropout rates from exercise RCTs in people with chronic kidney disease, we defined a high dropout as ≥ 25% of the study population.[4] Any participant who left the study at any time prior to completing the 12-week exercise program was defined as a dropout. Adherence was measured to assess patients' willingness to participate in IDE and to ascertain if the exercises were performed as per protocol (Table 1).

Response to the intervention

Acceptability of the exercises was defined as ≥50% of participants reporting that they would like to continue their current IDE program after study close. The change in physical activity performed outside of dialysis time was measured by self-reported questionnaire and using the Human Activity Profile (HAP).[20] To evaluate whether any participants adopted the other group's intervention (contamination) outside of dialysis time, patients' completed questionnaires on the types of activities performed in their leisure time at baseline at 12–weeks.

Qualitative interviews

Detailed information on participants and data collection methods can be found elsewhere.[21] To evaluate barriers to IDE implementation and to inform the content of staff in servicing, we interviewed dialysis unit staff three months prior to the start of the trial. To better understand the feasibility of unit staff participation in the delivery of the trial, unit staff members were also interviewed four months into the six-month trial. Unit staff were eligible to participate if the RCT directly affected their workflow and if they had worked in the unit during the trial. Interviews with RCT participants were conducted post-trial participation. All RCT participants were eligible if they were capable of sharing their experiences. Interviews were semi-structured with open-ended questions followed by specific prompts on aspects of feasibility. All interviews

were audiotaped and transcribed verbatim. For this analysis, interviews were coded using predetermined categories corresponding to our areas of feasibility and analyzed to yield a descriptive summary of study findings.

Secondary outcomes

Secondary outcomes were: QoL, (the physical component summary, [PCS] and the mental component summary [MCS]); tests of physical performance (Short physical performance battery, 30-second sit-to-stand test, and six-minute walk); an objective measure of strength; and AEs. Testing was carried-out at baseline and at 12 weeks, pre-HD on their scheduled HD day.

Quality of life

Participants completed The Kidney Disease Quality of Life Short Form (KDQOL-SF 36).[22] Item scores range from 0-100, with higher scores being more favorable. For this pilot, only the mean difference in PCS and MCS are reported.

Tests of physical performance

We used a range of tests to measure physical performance of the lower extremities. The Short physical performance battery (SPPB) includes: strength (five chair stands), endurance (4-meter gait speed) and balance (side-by-side, semi-tandem, and tandem). Each component is scored from 0 to 4 and is summed SPPB scores between 0 (poor) and 12 (best) performance.[23] The 6-minute walk test (6MWT) was used as a measure of aerobic capacity (distance walked reported in meters) and was performed according to recommendations from the American Thoracic Society.[24] To avoid a ceiling effect and to test muscle endurance, the number of complete getting-up and sitting-down repetitions performed in 30 seconds (STS 30 seconds) was also

tested.[25] Muscle strength was measured with the one repetition maximum (1-RM) test using a bilateral leg extension machine for the quadriceps.[26]

Adverse events

AEs were defined a priori and categorized as serious (death, cardiac event, hospitalization, disability, or any life-threatening event) or other (musculoskeletal injury, hypoglycemia, hypotension, hypertensive urgency [>200 mm Hg systolic or 110 mmHg diastolic], loss of consciousness, dialysis access complications, or any intervention by HD unit staff beyond minimal ultrafiltration). The primary analysis of AEs compared the frequency of events during the exercise session by randomization group. In a sensitivity analysis, all events occurring during the 12-week intervention period was planned. In both analyses, only the first event per individual was counted (for each type of adverse event).

Statistical analysis

We summarized baseline data using percentages, medians and inter-quartile range (IQR), or mean ± standard deviation (SD). For secondary outcomes, we explored the effect of aerobic and resistance exercise on QoL and tests of physical performance using the absolute change in score at 12 weeks relative to baseline. To attain the efficiency of the factorial design, all participants who received the aerobic intervention (cycling and the combined group) were compared to all those who did not (resistance and control exercise group) and a similar approach was used for the resistance-training group.[27] Analysis of covariance (ANCOVA) was used to adjust for the baseline score and the other intervention (main effect term).[28] To correct for multiple comparisons in the combined exercise group, the Bonferroni procedure ($P<0.025$) was used. We also estimated the confidence interval for the interaction term for the main study's primary outcomes.[27] Analyses comparing the groups at follow-up were conducted on an intention to

treat basis. Missing outcome data was imputed using a last-value carried forward approach. Data analyses were performed using Stata Statistical Software, version 13 MP software (www.stata.com).

RESULTS

This trial is reported according to the CONSORT guidelines [29] and the recommendations for good practice for the design and analysis of pilot studies.[30]

Participant flow

Of the 100 patients screened for eligibility, 36 did not meet inclusion criteria and 33 declined to participate (Figure 1). The most common reason for exclusion was inability to provide consent (n=8) and the most common reason for declining participation was 'no interest in exercising during dialysis' (n=11). Thirty-one participants were randomized and 26 completed the study: (cycling, n=7); (resistance training, n=6); (combined cycling and resistance training, n=7); (stretching n=6). Complete outcome data were available for 27 participants.

Baseline characteristics for RCT participants are shown in Table 2. Participants were predominantly male (77%), Caucasian (61%), with a median age of 57.6 years (IQR 49.2-75.1). The primary cause of ESRD was glomerulonephritis (32.3%) followed by diabetes (22.6%). Forty-eight percent of participants were diabetic, 90% had hypertension, and 26% had coronary artery disease, and 45% of trial participants were taking a beta-blocker. Overall, baseline physical functioning was low (mean PCS score of 35±8) and 39% of trial participants reported that they never exercised during their leisure time. Twenty-five of the 31 RCT participants participated in interviews (2 declined, 1 had a language barrier, and 3 changed location or dialysis modality).

The median age of patient interview participants was 57.5 years (interquartile range, [IQR] 49.2, 68.0); participants were primarily male (76%) and Caucasian (64%). Seven dialysis unit staff participated in pre-trial interviews (2 LPNs, 2 RNs, 2 service workers, and 1 technician); 86% were female. During the trial, 11 dialysis unit staff were interviewed (2 LPNs, 8 RNs, and 1 technician); 91% were female. Two dialysis unit staff participated in both sets of interviews.

Feasibility

Feasibility outcomes are shown in Table 1. To highlight key themes regarding the trial's feasibility, exemplar quotes from the interviews of staff members and patients are shown in Tables 3,4, 6, and 7.

Dialysis unit staff (pre-trial interviews): barriers to implementation and in servicing

Although none of the staff members who were interviewed had received any prior formal education on IDE, most staff were not interested in attending an educational session. The preferred means of obtaining more information on IDE were by reviewing "*scientific data*" in their own time. Several staff preferred a practical approach to in servicing and suggested that we focus on teaching them how to set up the exercise equipment and complete study documentation (Table 3).

All staff members described potential benefits of IDE, such as improved dialysis and leg cramps, weight loss, increased confidence, and patients "*keeping busy*." However, it was common for staff to express concern that for many patients in the unit, IDE would be unsafe or would interfere with aspects of the dialysis treatment (Table 3). Several staff also expressed concern that the exercise equipment would have a negative impact on their workspace.

Dialysis unit staff (pre-trial interviews): selection of suitable candidates

Several staff emphasized the importance of selecting appropriate patients for IDE, typically referring to those patients who were stable during HD or younger. Several staff members requested that prior to enrolling a patient, we discuss the patient's suitability for the trial with them. (Table 3)

Patients' decision to participate in IDE

Several staff stated that patients' social networks in the unit were an effective means of disseminating information. Another staff member stated that after being approached for study participation, patients commonly elicited their opinion (Table 3).

Based on the data from the pre-trial interviews, modifications were made to the study protocol (Box 1).

RCT participants: recruitment

We exceeded the target accrual of 28 subjects over 12 weeks. Randomization to exercise intervention was not a barrier to participation. Patient interview participants reported that recruitment posters displayed outside of the unit and hearing other participants discuss their participation in the trial were effective means of promoting interest and participation in the study (Table 4).

Dialysis unit staff (mid-trial interviews): fidelity to the protocol

Although the physical demand of delivering the exercise equipment to patients was not described as onerous, data collection for the trial was. One staff stated that there were occasions when trial documentation "*didn't get done*." Several staff reported that there were technical challenges with retrieving HR and BP data for DCFs from the HD machines. Some staff also mentioned that recording the vital signs was too time consuming.

Unit staff frequently made reference to the study as *"just one more thing"* and trial resource material was not frequently accessed. Although some staff members felt prepared to assist with the trial, several staff suggested that a lack of clarity on trial processes was a barrier to their involvement (Table 5).

RCT participants: fidelity to the protocol

The dropout rate over the study period was lower than our pre-specified threshold at 16%. Irrespective of exercise group allocation, patients' willingness to participate in IDE and their adherence to the exercise prescription was high: of the 1,038 training sessions offered, 87% of sessions were initiated (89% in the cycling group, 83% in the weights group, 90% in the combined group, and 86% in the stretching group). The exercises were performed as per protocol within all four groups for > 80% of exercise sessions (Table 1). Exercise parameters are shown in Table 6. For the active intervention groups, the mean RPE was within the targeted range and blood pressure and heart rate followed a similar trend: increasing during exercise and returning toward baseline post exercise. For the attention control, HR and BP were unchanged over the exercise period.

Although the exercises were protocolized, many participants viewed the intervention as tailored to their level (Table 5). Individualized instruction, progression based on RPE, and support from the kinesiologist[21] were commonly mentioned as strengths to the exercise program. For several patients, knowing there was the expectation of having to exercise facilitated adherence (Table 5).

Of the 1,038 exercise sessions that were offered, only three were terminated early. In all exercise groups, the most common reason for not initiating a given session was a physical complaint (7.5% of all prescribed sessions), commonly fatigue or feeling generally unwell. HD-related

issues accounted for only 1% of non-initiated sessions, primarily due to central venous catheter dysfunction. Many patients mentioned that consistently obtaining exercise equipment from unit staff was the main barrier to exercise participation;[21] however, this reason for non-participation was not captured with the exercise DCFs. Only 1.5% of DCFs had missing data for reason not initiated.

Dialysis unit staff (mid-trial interviews): impact of the intervention

Overall, dialysis unit staff agreed that the exercise program was valuable for patients (Table 7). Their perception of benefit was based on patient report, as the trial results were not known at the time of their interviews. Staff viewed patients' subjective improvements, such as 'feeling healthier' as valid evidence of the benefits of IDE (Table 7).

RCT participants: impact of the intervention

Across all exercise groups, the patients' response to exercise was highly favorable (Table 7); 92% of participants reported they wanted to continue IDE after the trial and 63% wanted to continue exercising with their current regimen (Table 1). There were no crossovers during the trial and no change in the amount of physical activity performed outside of HD time was detected. Concealment of stretching as an active treatment was successful among patients and staff. One participant in the attention control withdrew from the study because he did not find stretching beneficial, "*it wasn't straining, it was just too easy*." Although another participant stated that stretching was "*boring,*" most participants in the control group viewed stretching as an important aspect of an exercise regimen (Table 7). One participant commented that their exercise routine was shorter than the other groups resulting in relatively less interaction time with the kinesiologist.

Patients commonly discussed the benefits of IDE and for many, these results motivated them to continue exercising (Table 7). Patients discussed the exercise-related benefits of IDE, such as greater strength and endurance. Several patients attributed improvements in daily functioning to participation in IDE. Improvements in dialysis-related symptoms were also mentioned, primarily decreased cramping and restless legs. The most frequently discussed benefit of IDE was that it *"helped kill the four hours"* and that it made the time on dialysis more enjoyable. For one participant, IDE served as "*an escape from the humdrum*."

Secondary outcomes

The absolute differences in scores for secondary outcomes are shown in Table 8. Scores are presented as crude mean differences and main effects. No significant differences from baseline to 12 weeks were found in the PCS or MCS components of the SF-36 or physical performance tests (6MWT, 30 second STS, 1 RM). For the main effects analysis of the SPPB, the absolute difference in score and (95% CI) were 1.7 (0.2, 3.3) for the of all those allocated to receive cycling (cycling plus both interventions) versus no cycling (weights plus the attention control) and 1.6 (0.05, 3.2) for the main effect of those allocated to receive weights versus no weights. This result is consistent with a minimal clinically important difference (values from 0.5 to 1.3 have been recommended).[23,31] Interaction terms for the planned primary outcomes of interest for the main study were: PCS -4.2 (-16.1, 7.6); P=0.47 and SPPB -2.9 (-5.5, -.38); P=0.026.

No serious adverse events were reported during the exercise sessions. Due to the low frequency of events in the trial overall, comparative statistics were not performed. Adverse events occurring during exercise are shown in Figure 2. Two patients in the combined group had AEs (one dialysis access complication, one episode of hypertensive urgency and one episode of hypotension). Two patients in the cycling group had AEs (two episodes of hypertension and

ankle abrasions from the bike). In the weights group, there was one episode of access complication. There were no AEs during exercise in the stretching group. The overall frequency of AEs was low (Figure 3). Notably, there were two episodes of hypotension in the control group, three in the cycling group, and one episode in the weights and combined exercise group.

Discussion

The purpose of this pilot study was to evaluate the feasibility of an IDE exercise intervention and to perform an exploratory analysis of cycling and weight training each compared with control on QoL, tests of physical performance, and strength. We demonstrated feasibility of recruitment and high patient acceptability. In addition, few exercise trials in this population have attempted to blind participants to group allocation.[4] We demonstrated a low risk of contamination and attrition with the use of an attention control and blinding to study hypothesis. However, primarily based on the findings from the interviews with dialysis unit staff and trial participants, several modifications to the study protocol are required prior to proceeding with the main study.

Readiness for change is considered critical to the successful implementation of complex interventions in healthcare settings.[32] In this pilot, we found that there was a lack of readiness among dialysis unit staff for IDE. Several of the factors that influenced unit staff's preparation, motivation, and ability to participate in this trial have been cited in other studies as barriers to the implementation of clinical IDE programs: lack of time,[33,34] high patient care demands,[35] and safety concerns with the exercise equipment in their workspace [33]. In our previous study, we also identified a lack of support from management and personal beliefs about exercise as influencing staff readiness for IDE.[21] Therefore, prior to recruitment for the main study, it will be necessary to develop a strategy for understanding staff readiness at potential study sites. Although the influence of education on staff participation in IDE remains unknown, in one study,

patient and staff thought that a better understanding of IDE would have improved their initial participation.[35] In this pilot, the lack of interest among many unit staff for IDE education was a barrier to engaging staff. Other more convenient forms of delivering education i.e. videos online and reading material on the unit were not highly accessed. As unit staff expressed that seeing and hearing the benefits from their patients first-hand positively influenced their perceptions of the intervention, a pre-trial demonstration phase may be the most effective means of promoting acceptability of IDE. Despite the concerns expressed in the pre-trial interviews about patient and workspace safety, that no unit staff mentioned these concerns in the second set of interviews (once the intervention was established), also supports the value of providing staff with the opportunity to experience IDE in their own setting prior to study start.

In addition to requiring the unit staff's assistance with IDE delivery for practical reasons, we identified other reasons why their participation was important. First, due to their frequent and prolonged contact with patients, dialysis unit staff are in a unique position to assist patients with decision-making.[36] As we found that some patients seek the opinion of dialysis unit staff on study participation, it is important that those who engage in these discussions are prepared to discuss the risks and benefits of IDE with patients. Although 30% non-participation is comparable to other trials in this population,[16,18,19,37] it is possible that the staff's perceptions of IDE influenced patients' decision to participate. Second, the patients' perspective that unit staff's assistance and encouragement with IDE is consistent with their role as carer and patient advocate has the potential to influence patient acceptability of IDE.[21] Third. many patients experienced difficulty consistently obtaining exercise equipment from unit staff, which has clear implications for patient adherence.[21]

For unit staff, exercise data collection was too time consuming and resulted in missing data. This issue was recognized early in the trial and resolved with greater involvement from study staff. This strategy is not feasible for a multisite study and exercise vital signs will be limited to pre-, mid-, and post-exercise. We also found that for unit staff, feasibility of workflow integration was affected by the timing of when in the dialysis treatment that IDE was performed.[21] To decrease the risk of hypotension, other trials have typically completed exercise within the first one to two hours of the HD session [16,38,39] and starting exercise within the first hour of HD is often recommended. However, this is often the busiest time for unit staff and in settings where there are staffing constraints it may be a barrier to optimal staff engagement. We are only aware of one trial where IDE was performed in the final two hours of the HD session and this was well-tolerated.[40] Our protocol specified that patients finish their exercise within the first 3 hours of the dialysis shift. The safety of this approach is supported by our blood pressure and safety data. A more detailed evaluation of the timing of the HD session and its effect on blood pressure would provide important insight into how to optimize both the safety and the practicality of IDE delivery.

This study has several important strengths. Most studies evaluating exercise adherence in people with kidney disease have focused on individual determinants and not evaluated program factors.[41,42] In this study, progression based on RPE and individualized instruction facilitated acceptability among patients. As described in our qualitative study, patients perceived the kinesiologist's technical support as conveying a sense of esteem and capability.[21] This interaction may have served to increase participation, irrespective of group assignment. Additionally, the most commonly mentioned benefit to IDE was that it helped pass the time, suggesting that many patients are interested in participating in interventions where they can use their time on HD more constructively. It also suggests that some of the perceived improvement

in wellbeing could be mediated through engagement in an activity, rather than exercise. These findings underscore the importance of continuing to use a supervised attention control for the main study. Our study also has several limitations that warrant mention. Given the potential impact of the interaction with the exercise specialist on IDE acceptability, it will be important to ensure that the interaction time between the attention control group and the kinesiologist is equivalent to that of the intervention groups. Also, the trial study population was small and relatively homogeneous with respect to sex, age, and ethnicity, which may limit the generalizability of the findings.

We did not detect differences in physical activity or exercise performed outside of the unit during the trial, nor was the trial powered for this outcome. The antagonistic interaction term for the SPPB will also need to be explored in more detail, as this could be a spurious finding due to multiple outcome testing. The primary aim of this pilot study was to evaluate feasibility and small sample sizes were used. Therefore, the finding that cycling or weights did not improve QoL or other measures of physical performance should not be interpreted as providing evidence for no effect. Based on 80% power to detect a difference in the primary outcome of PCS of 5 points[43] in the main effect of aerobic and the main effect of resistance, 32 participants per arm are required. Allowing for 25% dropout per arm, the main study will enroll 160 patients. A four-arm parallel design would allow direct comparisons between the interventions; however, the sample size would need to be at least twice as large as that calculated for the main study. Given that recruitment and retention are barriers to performing adequately powered exercise studies in this population, the factorial design is one means of improving efficiency while allowing for indirect comparisons between aerobic and resistance training.

Conclusions

To our knowledge, this is the first feasibility study to use qualitative methods to evaluate IDE implementation within an RCT design and to address known limitations to trial design. In addition to informing the design of our future definitive study, these results are useful in the development of future trials and for guiding clinicians with the implementation of their own IDE interventions. The key lesson learned was that within this protocolized setting, the potential for unit staff readiness to influence aspects of feasibility, such as recruitment and patient adherence was high. Therefore, prior to study start, more time will need to be invested in understanding and enhancing staff readiness. For engaging unit staff, a less didactic approach that is also integrated into their existing workflow may be highly effective.

Authors' contributions

Authorship followed ICMJE guidelines. ST was responsible for the inception and design of the project and prepared the manuscript. MH, SK, AM, and MT participated in the design of the study and provided methodological input. IG participated in the design of the exercise intervention. AL provided statistical support. All authors read and approved the manuscript.

List of abbreviations

End-stage renal disease (ESRD); rating of perceived exertion (RPE); Intradialytic exercise (IDE); Hemodialysis (HD); Quality of life (QoL); Randomized controlled trial (RCT); Data collection form (DCF); Adverse event (AE); PCS (physical component score); MCS (mental component score); SPPB (short physical performance battery); 6MWT (6-minute walk test); STS 30 seconds (30-second sit-to-stand); 1-RM (one repetition maximum): Heart rate (HR); Blood pressure (BP); inter-quartile range (IQR); standard deviation (SD).

Competing interests

The authors have no competing interests to declare.

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Table 1: A priori feasibility criteria and outcomes

Feasibility criteria	Feasibility outcome
Recruitment	
Accrual: 28 participants over 12 weeks	31 participants over 12 weeks
Reason for non-participation: proportion of screened patients unwilling to be randomized must be ≤ 20%	No patients reported randomization to exercise type as a reason for non-participation.
Fidelity to the protocol	
Drop-out: ≤ 25% of study participants withdrawing participation	**16% of participants dropped out:** Cycling n=1, transplanted Resistance n=1, injury from motor vehicle collision Combined n=1, moved dialysis unit Attention control n=2, nausea and vomiting; did not like exercise
Adherence (willingness of participants to participate): of all exercise sessions offered,[1] ≥ 70% were initiated	**87% of prescribed exercise sessions were initiated:** Cycling 89% Weights 83% Combined 90% Attention control 86%
Adherence (accordance with the exercise prescription): of all exercise sessions offered, ≥ 70% were performed at the prescribed time/volume and intensity	**86% of prescribed exercise sessions were performed as prescribed:** Cycling 87% Weights 84% Combined 88% Attention control 86%
Impact of the intervention	
Acceptability of the exercises: overall ≥50% of participants reporting that they would like to continue their current intradialytic exercise program after the study is over	**63% of participants said they would continue with their current exercise** Cycling 50% Weights 50% Combined 100% Stretching 38%
Change in the amount of physical activity performed overall: difference in the HAP scores between baseline and 12 weeks[2]	MAS: Cycling versus no cycling 4.3 (-2.8, 11.5) P=0.3 Weights versus no weights -1.2 (-8.4, 6.0) P=0.7 AAS: Cycling versus no cycling 1.1 (-7.7, 9.9) P=0.8 Weights versus no weights -0.9 (-9.7, 7.8) P=0.7

Difference in the proportion of participants who reported never exercising outside of HD time	Baseline: 39% of participants exercised almost never or never exercising versus 12 weeks: 29% of participants exercised almost never or never (P= 0.55)
Contamination: any participant who adopted the exercise(s) of another intervention group during the study period	No participants from the cycling, weights, or stretching groups reported performing the other group's exercise

HAP (Human Activity Profile); MAS (maximal activity score); AAS (adjusted activity score).

1. Offered sessions exclude sessions lost to study dropout. 2. Analysis performed for main effects adjusting for the baseline score and other factor.

Figure 1: RCT participant flow

Table 2: Baseline characteristics of trial participants

	All (n=31)	Cycling (n=8)	Weights (n=7)	Combined (n=8)	Stretching (n=8)
Age[1]	57.6 (49.2-75.1)	66.9 (55.8-82.4)	59.7 (45.9-81.4)	60.3 (54.7-68.4)	49.3 (43.0-62.3)
Sex (male)	24 (77)	8 (100)	6 (86)	3 (38)	7 (88)
Time on HD (yrs)	3.2 (1.7-4.4)	3.7 (2.4-4.6)	2.8 (2.0-4.0)	2.9 (0.7-2.3)	3.3 (1.2-6.2)
Ethnicity					
Caucasian	19 (61)	7 (88)	3 (43)	5 (63)	4 (50)
Southeast Asian	4 (13)	1 (13)	1 (14)	1 (13)	2 (25)
Aboriginal	3 (10)	0	2 (29)	0	1 (13)
Other	5 (16)	0	1 (14)	2 (25)	1 (13)
Cause of ESRD					
Diabetes	7 (22.6)	2 (25)	1 (14.3)	2 (25)	2 (25)
Glomerulonephritis	10 (32.3)	1 (12.5)	5 (71.4)	4 (50)	0
Hypertension	1 (3.2)	1 (12.5)	0	0	0
Polycystic kidney disease	3 (9.7)	1 (12.5)	0	1 (12.5)	1 (12.5)
Reflux/urological	3 (9.7)	1 (12.5)	0	0	2 (25)
Other	5 (16.1)	2 (25)	1 (14.3)	0	2 (25)
Unknown	2 (6.5)	0	0	1 (12.5)	1 (12.5)
BMI	24.7 (21.6-29.9)	23.6 (22.2-25.7)	25.9 (24.6-29.9)	25.3 (20.0-30.8)	24.2 (20.4-33.8)
Diabetes	15 (48)	3 (38)	3 (43)	5 (63)	4 (50)
Hypertension	28 (90)	8 (100)	7 (100)	7 (88)	6 (75)
Beta blocker	14 (45)	4 (50)	4 (57)	3 (38)	3 (38)
Coronary artery disease	8 (26)	4 (50)	1 (14)	2 (25)	1 (13)
Heart failure	7 (23)	4 (50)	3 (43)	0	0
QoL-PCS	35 ± 8	35 ± 9	32 ± 9	35 ± 10	36 ± 3
Never exercise in leisure time	12 (39)	3 (38)	4 (57)	1 (13)	4 (50)

1. Median (IQR interval); N with (%) or mean (± standard deviation); totals do not always add to 100 due to rounding

Table 3: Quotes from pre-trial interviews with dialysis unit staff

Barriers to implementation and in servicing
In servicing *"I would prefer to read, it's easier. And to have it always in my pocket--a reference."* *"As long as we know what—where the documentation's required; I don't think anything else to be honest with you"* ***Patient safety and staff workflow*** *"The other thing you're going to have is once the patients start moving about, if they've got their fistula access, it is going to be compromised, and I would not compromise that."* *"They could slip out of their chair; they're not sitting properly, they could split their shin with it because they're diabetic, that could cause problems for them…"* *"And we are very, very busy, [at changeover] and nothing's supposed to be around us because we're running from machine to machine to get ready for the next patient."*
Selection of suitable candidates
"Some young people [would be good for IDE] …But I cannot say how many. *"I think just being very careful who you pick for the study. It has to be somebody who's physically able to do it, mentally competent. Some people might seem like they're physically able, but they're not mentally able."* *" Actually, [pause] just asking for input on patients to make sure that they are suitable...Or even before you ask them, make sure they are suitable for that program [IDE}. Because I mean, there's a lot of patients they aren't stable and their blood pressure will drop..."*
Patients' decision to participate in IDE
"So I think because a lot of them are friends here, so they talk, and, you know, if you're doing that, "What do you think about it?" So they ask each other. Or they can even do it together if they're sitting side-by-side; you know, "Oh, that's kind of fun."... 'Cause a lot of things happen that way here, 'cause they listen to what other patients talk to nurses about, then they think, "Oh, okay, I'll try that, too." *"After the conversation with research person, they usually ask our opinion."*

Box 1: Modifications to the study protocol following pre-trial interviews with unit staff

Trial protocol item	Initial plan/barrier	Modification
In-servicing format	Didactic sessions on the benefits of exercise in people with ESRD and one practical session with the exercise equipment	Two practical in-services on study procedures and equipment set-up Video posted on YouTube on the exercises and how to assist patients with equipment set-up Education materials (articles, pamphlets, summaries) on IDE placed on the unit for staff
Workspace safety for staff	Exercise equipment as workspace hazard	Unit staff identified where equipment would be stored on the unit With unit staff input, protocols for equipment set-up and removal were written into study protocol
Recruitment	Only study staff selects suitable candidates	Prior to enrolling a patient, the charge nurse was consulted regarding any dialysis-related safety concerns
Implementation	Include several unit staff members as volunteer "exercise champions" to lead unit staff and liaise with study staff	No volunteers found. Identified four staff "point people" who were already in leadership roles in the unit to informally check in with study staff on trial implementation

Table 4: Exemplar quotes from RCT participants on trial recruitment

Patients' decision to participate in IDE
"No, hadn't thought about—well, I saw the posters and thought, "Hm, interesting. Maybe… I hadn't figured you could do anything...[on dialysis]."
"First of all, it was a novelty, and then it was interesting to see how it was a wave of interest; it was a domino effect. And there was a real nice buzz... The [other] patients were, "Hey, you're doing—what are you doing?" etc., etc., so that was super.

Table 5: Exemplar quotes from interview participants on fidelity to the protocol

Dialysis unit staff (mid-trial interviews)
"...we check patients every half-hour for their blood pressures and all the dialysis machine readings and stuff like that, so I find also recording the blood pressure is very time-consuming, because we can go back and look at the list of blood pressures on their machine after, but then we just go back and find them or you have to be recording them every 5 or so minutes, so you're running back and forth between doing your other work and so forth. So I find it's very busy in that respect." *"It was just difficult to add something for us to do, 'cause initially, I think what the thought was to teach all the nurses what the patients were supposed to be doing, but it was just difficult to in-service everybody. They were, like, "Okay, so this is how you fill out the sheet"—'cause the sheet, to me, I'm so confused working with it. And sometimes—oftentimes, we're short-staffed, so we don't have the staffing to even get this equipment and all that kind of stuff. So it ended up being they just ended up coming every run and doing the exercise study with the patients. ... I think there was a lot of resistance from staff to really help out with it."* *"I am prepared because they also have an in-service, and they also have [the kinesiologist] here to show us, she also give us e-mail and show with the video, show us how the exercise going. But I be honest, we don't have time to look at that. We don't have time to sit down and look at that video!"*
RCT participants (post-trial participation)
"Yes, because I was starting from zero exercise, so I wasn't sure how much, how hard it would get, how—if I could keep up to what they wanted, that kind of thing...But they did it very gradual, and [the kinesiologist] was very good about telling us ahead of time when they're going to put up the weights or when they're going to increase the minutes of pedaling, so you knew what to expect." *"Well, we were increased at our own pace, which I really liked, because I just went at my own level."* *"Also I want to tell you that I have a treadmill at home, but sometimes I do it, sometimes I don't. But here, it's, like, we have to..."*

Table 6: Exercise parameters for the four exercise groups

	Cycling	Weights	Combined	Stretching/control
Borg (Intensity, RPE)	13 ± 1	13 ± 1	13 ± 1	8 ± 2
Mean amount of exercise performed	28.0 ± 3.4 minutes	36 ±12 (repetitions) 5.0 ± 3.4 (lbs)	27.5 ± 8.8 minutes; 35 ± 12 (repetitions) 3.7 ± 1.8 (lbs)	NAP
Systolic BP (mmHg)	Pre: 136 ± 20 During: 150 ± 26 Post: 130 ± 21	Pre: 123 ± 26 During: 127 ± 27 Post: 117 ± 26	Pre: 121 ± 28 During: 126 ± 24 Post: 116 ± 26	Pre: 119 ± 22 During: 119 ± 22 Post 118 ± 20
Diastolic BP (mmHg)	Pre: 74 ± 16 During: 80 ± 19 Post: 75 ± 16	Pre: 66 ± 15 During: 67 ± 16 Post: 63 ± 15	Pre: 62 ± 13 During: 67 ± 13 Post: 63 ± 13	Pre: 70 ± 14 During 70 ± 15 Post 69 ± 14
Heart rate (bpm)	Pre: 66 ± 14 During: 85 ± 20 Post 77 ± 17	Pre: 71 ± 12 During: 78 ± 13 Post: 74 ± 13	Pre: 69 ± 11 During: 79 ± 13 Post: 73 ± 11	Pre: 78 ± 17 During: 77 ± 16 Post: 77 ± 17

RPE (rating of perceived exertion); BP (blood pressure); HR (heart rate); bpm (beats per minute); lbs (pounds).

Pre, post, and during exercise BP and HRs are a means ± SD for initiated exercise sessions.

Table 7: Exemplar quotes from interview participants on the impact of the intervention

Dialysis unit staff (mid-trial interviews)
The benefits of IDE *"A lot of them—well, I think probably all of them increased their muscle mass and they have more strength at the end of the program, so they were quite pleased."* *"So yeah, the patients, I find, like the ones on the study feel good about themselves. They feel good, and I think they feel better…"*
RCT participants
Acceptability of the exercises *"I thought it was—everything was set up perfectly for me. I could do each exercise. Of course, it's a little cumbersome doing a few of the leg reps in a chair, but it's not insurmountable, by far."* "*Well, because all I had to do was the stretches, in a way, it was kind of boring, I think. But it's not like stretches aren't good for you; I mean, it is, they're good for you. But I don't know, it's just—it was alright; I wouldn't say it was all that exciting or anything."* *"…I was quite amazed that even with the stretchy bands—and it's a good thing I started with those to kind of loosen me up a little, because I was—like, I had muscles that were sore..."* ***The benefits of IDE*** *"I'm more steady on my feet. My legs were pretty shaky before, and now they're not."* *"..even my wife has noticed I've got more muscle tone on my legs. And I was really surprised about that, 'cause I didn't think dialysis patients could—and especially even at my age get that kind of deal. But I even noticed myself, I do have more muscle tone."* *"…Like, I do a fair amount of walking, myself, probably 12 blocks a day, and so my legs were fairly good, but I cannot keep up to my wife if we went shopping. Now I can."* *"Oh, I get cramps. Every dialysis run, I had cramps, but after doing exercise, I—no more cramps now."* *"I had restless leg, and I still have it, but surprisingly, not as drastic..."*

Table 8: Secondary outcomes (QoL, tests of physical performance, and strength)

Outcome	Cycling (n=8)	Weights (n=7)	Combined (n=8)	Stretching/control (n=8)
PCS; mean difference & SD	5.2 ± 9.3	4.1 ± 8.0	1.7 ± 7.4	3.4 ± 7.3
Main effects (95% CI)	Cycling vs no cycling -0.076 (-5.9, 5.8); P=0.979		Weights vs no weights -1.82 (-7.7, 4.1); P=0.53	
MCS; mean difference & SD	-2.3 ± 10.7	-3.4 ± 9.1	-1.5 ± 5.9	0.70 ± 7.5
Main effects (95% CI)	Cycling vs no cycling 0.23 (-6.0, 6.5); P=0.94		Weights vs no weights 0.21 (-6.5, 6.9); P=0.95	
SPPB; mean difference & SD	1.9 ± 2.4	1.4 ± 1.9	1.0 ± 1.2	0.63 ± 1.2
Main effects (95% CI)[1]	Cycling vs no cycling 1.7 (0.2, 3.3) P=0.028		Weights vs no weights 1.6 (0.05, 3.2) P=0.044	
6MWT; mean difference & SD	42.3 ± 88.8	54.9 ± 52.9	39.0 ± 76.8	0.8 ± 44.0
Main effects (95% CI)	Cycling vs no cycling 12.8 (-36.1, 61.6) P=0.60		Weights vs no weights 30.7 (-17.8, 79.2) P=0.21	
STS 30 seconds; mean difference & SD	0.9 ± 2.2	1.6 ± 2.7	1.4 ± 3.5	1.4 ± 4.3
Main effects (95% CI)	Cycling vs no cycling -0.31 (-2.7, 2.1) P=0.79		Weights vs no weights 0.42 (-2.0, 2.8) P=0.73	
1-RM; mean difference & SD	11.6 ± 10.7	8.9 ± 5.5	4.9 ± 11.6	9.3 ± 10.1
Main effects (95% CI)	Cycling vs no cycling -3.4 (-11.0, 4.2) P=0.37		Weights vs no weights -2.8 (-9.9, 4.2) P=0.42	

PCS (physical component score); MCS (mental component score); SPPB (short physical performance battery); 6MWT (6-minute walk test); STS 30 seconds (30-second sit-to-stand); 1-RM (one repetition maximum)

Models are adjusted for baseline score and the other main effect term. 1. Interaction term included in the model (P=0.026)

Figure 2: Adverse events occurring during the exercise session

Dialysis access complications= re-needling, hematoma

Figure 3: Adverse events occurring over the study period

Dialysis access complications= re-needling, hematoma

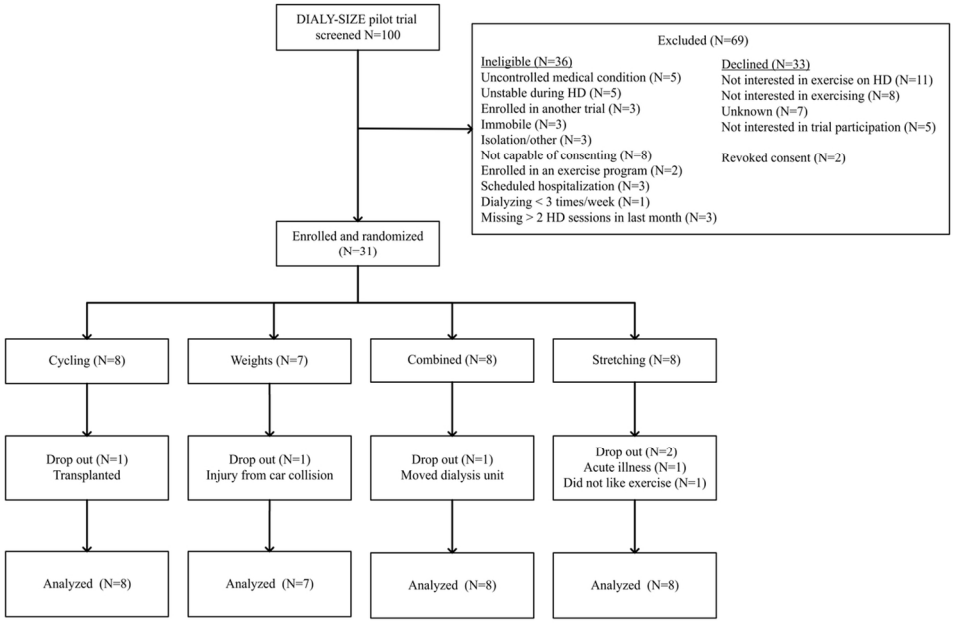

Figure 1:RCT participant flow

118x81mm (300 x 300 DPI)

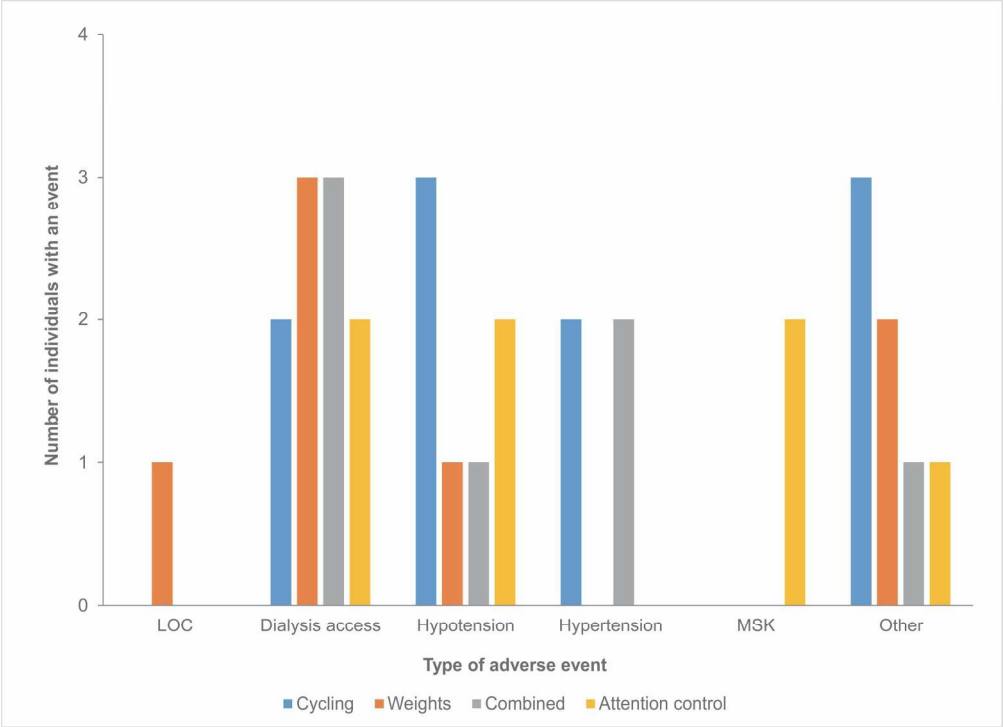

Figure 3: Adverse events occurring over the study period

173x125mm (300 x 300 DPI)

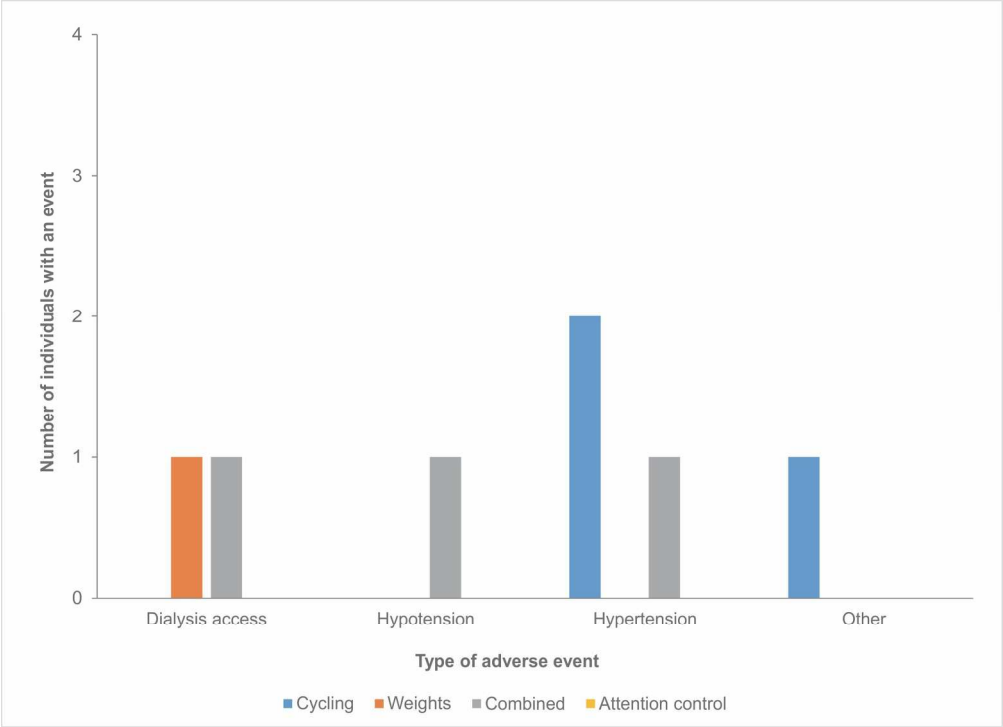

Figure 2: Adverse events occurring during the exercise session

173x126mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Title page
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NAP
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NAP
Sample size	7a	How sample size was determined	22
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NAP
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
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	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NAP
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NAP
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13 (and figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	13 (and figure 1)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	No
	14b	Why the trial ended or was stopped	NAP
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 13 and Table 8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 18-19 & table 8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NAP
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NAP
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Page 19 & Fig 2 &3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 22-23 & 4
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Page 20-22
Other information			
Registration	23	Registration number and name of trial registry	Page 3
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 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.

NAP=not applicable
NA=not available