Addressing Knowledge Gaps in Intradialytic Exercise

by

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ABSTRACT

End-stage renal disease (ESRD) requiring hemodialysis (HD) is associated with poor health outcomes including low quality of life and physical functioning. The association between quality of life (QoL), mortality and hospitalization is well established; however, few interventions have been shown to improve QoL in this population.

Regular exercise is a promising therapeutic tool for decreasing the disease and treatment-related burden imposed by ESRD. As the majority of people with ESRD receive HD in a hospital or facility three times per week, delivering exercise during the HD treatment (intradialytic exercise, [IDE]) is an opportunity to increase exercise participation. However, in contrast to other chronic diseases, outpatient exercise programs for people with ESRD have not been adopted into routine practice. In part, the underuse of exercise in practice can be explained by key knowledge gaps: limited data on the relative benefits and risks of different types of exercise in people with ESRD, methodological limitations in trial design, and the lack of attention to the practical challenges and complexity of delivering an exercise program during the HD treatment.

Based on these knowledge gaps, this three part, mixed-method thesis investigates how to increase the uptake of IDE. First, to evaluate the feasibility of a main efficacy trial aimed at evaluating two types of IDE (cycling and resistance) on QoL and physical performance, a mixed-method, randomized factorial pilot trial was conducted. Second, to understand the factors that influence IDE implementation, concurrent with the trial, a qualitative interpretive descriptive study was conducted. Third, to evaluate how the complex and variable aspects of an IDE program influence patient participation in IDE, a study protocol has been proposed where the realist line of inquiry

will be used to synthesize knowledge from a literature review and interviews with IDE stakeholders worldwide.

The main findings from the pilot trial were: feasibility of recruitment, high patient acceptability, and low measures of contamination and attrition with the use of an attention control. Progression based on perceived exertion and individual instruction facilitated acceptability of the intervention among patients. There were no serious adverse events and the frequency of other adverse events, including hypotension and vascular access dysfunction was low across all groups. Intervention effects on the secondary outcomes (QoL, physical performance) were not statistically significant. Beyond the need for practical assistance with IDE delivery, staff engagement with IDE was necessary to maintain the integrity of the intervention and was also perceived by patients as important. However, due to factors at the individual and system level, there was a lack of staff readiness for IDE. These factors were explored further in the qualitative study. Common themes from patient and staff interviews were: support, norms (expected practices) within the dialysis unit, and the role of the dialysis nurse. Staff described a lack of support from management and the additional theme of "no time" (for staff to participate in IDE) was influenced by its low priority in their workflow and the demands of the unit. Staff focused on the technical aspects of their role in IDE while patients viewed encouragement and assistance with IDE as the staff's role. The support of the kinesiologist enhanced patients' sense of capability and was a key component of implementation as was delivering IDE in keeping with unit norms. The staff's emphasis on patients setting-up their own equipment and enhanced social interaction among trial participants were additional themes that conveyed the unintended consequences of the intervention.

These findings provide guidance to researchers, clinicians, and renal program administrators on IDE implementation. To improve trial design, researchers should consider using novel methods of blinding and evaluating adverse events that are relevant to IDE. Staff readiness for IDE could be improved with better workflow integration, greater support from management, better understanding of staff's personal values of exercise, and by understanding priorities and values within the unit as a whole. Incorporating social support into IDE interventions could increase their effectiveness and greater social interaction among IDE participants is a potential means of improving patients' satisfaction with HD care. Findings from the realist synthesis extend this work by identifying where and how to resources could be allocated to an IDE program so that it is more likely to be effective in increasing patient participation.

PREFACE

This thesis is an original work by Stephanie Thompson. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board:

Chapter 3, "Exercise in the dialysis unit: a randomized factorial pilot study on the feasibility and safety of intradialytic exercise (*DIALY-SIZE!);*"No. Pro00036420; April 24, 2014.

Chapter 4, "A qualitative study of an intradialytic exercise intervention;"No. Pro00046639; March 11, 2014.

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A version of Chapter 3 of this thesis has been submitted for publication to *Implementation Science* as S. Thompson, S. Klarenbach, A. Molzahn, A. Lloyd, M. Haykowsky, I. Gabrys, and M. Tonelli, "A randomized factorial mixed-method pilot study of aerobic and resistance exercise in hemodialysis patients: *DIALY-SIZE!*" I was responsible for the inception, design, and analysis of the study. I oversaw the day to day operations of the trial was responsible for the composition of the manuscript. SK, AM, and MT participated in the design of the study, provided methodological input, and contributed to manuscript revision. IG and MH participated in the design of the exercise intervention and IG contributed to manuscript edits. AL provided statistical support and contributed to manuscript revision.

Chapter 4 of this thesis has been accepted for publication as S. Thompson, M. Tonelli, S. Klarenbach, A. Molzahn, "A qualitative study to explore patient and staff perceptions of intradialytic exercise" *Clinical Journal of the American Society of Nephrology,* accepted February 23, 2016. I was responsible for the inception, design, and analysis of the project and manuscript composition. AM provided methodological input and participated in the analysis. MT, SK, and AM participated in the design of the study and contributed to manuscript revision.

Chapter 5 of this thesis has been accepted for publication as S. Thompson, A. Clarke, A. Molzahn, S. Klarenbach, and M. Tonelli, "Increasing the uptake of exercise programs in the dialysis unit: a protocol for a realist synthesis" *Systematic Reviews*, accepted February 10, 2016. I was responsible for the inception and design of the project and prepared the manuscript. AC, SK, AM and MT participated in the design of the study, provided methodological input, and contributed to manuscript revision.

DEDICATION

This thesis is dedicated my husband, Mike whose constant support, sense of humor and balance made this attainable. A special thanks to my mother in law, Mary M. whose support helped keep us all more rested, fed, and happy. Also thanks to my parents and sister, for their support.

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This connection provided additional opportunities for discussion and collaboration throughout my training.

I would also like to thank the local chapter of the National Kidney Foundation (Northern Alberta and the Territories). This organization has committed to assisting with the development of intradialytic exercise programs within the Northern Alberta Renal Program.

Finally, I would like to express thanks to the participants of this work for their time, commitment, and openness.

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LIST OF ABBREVIATIONS

ESRD	End-stage renal disease
HD	Hemodialysis
QoL	Quality of life
IDE	Intradialytic exercise
RRT	Renal replacement therapy
RCT	Randomized controlled trial
CKD	Chronic kidney disease
AEs	Adverse events
6MWT	6-minute walk test
STS 30 seconds	30-second sit-to-stand
K/DOQI	Kidney Disease Outcomes Quality Initiative
RPE	Rating of perceived exertion
SD	Standard deviation
IQR	Interquartile range
DCF	Data collection form
PCS	Physical component score

MCS	Mental component score
SPPB	Short physical performance battery
One repetition maximum	1-RM
Blood pressure	BP
Heart rate	HR
KDQOL-SF 36	The Kidney Disease Quality of Life Short Form
Context-Mechanism-Outcome	CMO
NARP	Northern Alberta Renal Program
KT	Knowledge Translation

CHAPTER 1- INTRODUCTION

1.1 Statement of the problem

In Canada, the prevalence of patients with end-stage renal disease (ESRD) receiving dialysis has increased by 40% over a ten-year period, with approximately 24,114 people requiring dialysis in 2013.[1] Hemodialysis (HD) provided in a facility continues to be the most common form of renal replacement therapy (RRT), which accounts for a disproportionate amount of healthcare spending. The estimated cost of in-center hemodialysis on a thrice-weekly basis is $120,000 per patient per year.[2] This does not include the cost of the frequent and prolonged hospitalizations[3] or the frequent dialysis-related procedures[4] that occur in this population.

Despite this high spending, health outcomes in this population are poor with a crude annualized mortality of 18%, primarily due to cardiovascular disease.[5,6] Quality of life (QoL) is also highly compromised: someone with a 10 year life expectancy on dialysis would be willing to give up 4 years of life to have normal kidney function.[7] Although there is clearly much room for improvement in the treatment of people with ESRD, randomized controlled trials of interventions aimed at improving mortality in this population have mainly been negative, even for interventions that have been effective in the general population.[8–13] The nephrology community's response to these negative trials has been mixed, including calls for the evaluation of multi-pronged interventions, improved trial design, and also cynicism about the potential to improve mortality in ESRD—or 'renalism.'[14] Perhaps one positive consequence of the uncertainty on how to improve 'hard outcomes' in this population is the increased recognition that other clinically important outcomes, such as those reported by patients are important and attainable targets for improvement.

In the context of healthcare, QoL is a multidimensional concept, obtained by patient report, which includes physical, social, and psychological domains. Disease-specific measurements of QoL can be used to evaluate the impact of disease and treatment-related factors. It is well-established that QoL among people with ESRD is low and the associations among mortality, hospitalization and QoL underscore the significance of evaluating QoL measures.[15,16] Furthermore, for people with end-stage renal disease (ESRD) and their care-givers, finding interventions to reduce the physical, social, and psychological impact of kidney disease is a top research priority.[17] Given that the average age and comorbidity burden of patients starting HD is increasing, finding effective treatments to improve QoL and maintain physical functioning will become an increasingly important clinical and economic issue.

In people requiring HD, regular exercise is a promising therapeutic tool for improving aspects of QoL as well as several cardiovascular parameters and exercise tolerance.[18–21] However, in contrast to other chronic disease models (i.e., those used in cardiology and pulmonary medicine), outpatient exercise programs for people with ESRD have not been adopted into routine practice. While the current research on exercise in ESRD has advanced knowledge on the efficacy of exercise in this population, the limited uptake of exercise programs in nephrology practice can be explained by existing gaps in the literature. These gaps include a lack of evidence to inform implementation and uncertainty on what exercise to recommend to patients for optimal benefit while reducing risk.

1.2 Study Objectives

The purpose of this three-component mixed-method thesis is to investigate how to increase the uptake of exercise in clinical practice by addressing critical knowledge gaps on the implementation, feasibility, efficacy, and safety of exercise in people requiring HD. This thesis focuses on exercise prescribed during HD (intradialytic exercise, [IDE]) as integrating exercise into the regular treatment plan is an opportunity to evaluate the implementation of exercise into routine care.

The specific objectives of this thesis were:

i. To evaluate the feasibility of an efficacy trial aimed at comparing two types of intradialytic exercise (cycling and resistance) with control.

ii. To explore differences between intervention groups in health-related quality of life, physical function, strength, and adverse events on quality of life, physical performance, strength, and adverse events.

iii. To describe perceptions of IDE from the perspectives of those delivering and receiving the intervention and to understand the factors that influence implementation.

iii. To develop theories that explain how contextual factors work to influence patient participation in clinical IDE programs.

iv. Based on the above theories, to develop general recommendations for research users on where and how resources could be allocated to the IDE program so that it is more likely to attain its intended health outcomes.

1.3 Thesis submitted for partial fulfillment of PhD

This thesis consists of a literature review on exercise in people with ESRD (Chapter 2) and three studies (Chapters 3-5), each designed to address the objectives from section 1.2. In order to adequately evaluate the complexity of IDE delivery and to increase the relevance of the findings within the wider context of nephrology care, qualitative methods are used in each of the three studies. The final chapter (Chapter 6) contains a summary of the key findings from each study and a discussion on the implications and impact of this work.

The literature review in Chapter 2 begins with a definition of ESRD, an overview of the treatment, and a brief discussion on what is known about the impact of this illness on patients' QoL. In subsequent sections, the exercise literature in people with chronic kidney disease (CKD) is reviewed, focusing on the ESRD population and interventions delivered during the HD treatment. Important considerations in the interpretation of this evidence, findings from systematic reviews and randomized controlled trials (RCTs) on exercise in people with kidney disease, and the significance of commonly evaluated trial outcomes are described. The review of the effect of exercise on specific outcomes in Sub-sections 2.2.4-2.2.6 is not exhaustive; the discussion is limited to those outcomes that are relevant to this work. Chapter 2 also contains a review of the barriers and facilitators to exercise participation for ESRD patients and for renal care-providers, barriers and facilitators to exercise promotion. Studies that have investigated the influence of exercise setting (home, intradialytic, or in-center on a non-HD day) on trial outcomes and adherence are also reviewed. In Section 2.5, the rationale for IDE is discussed in terms of its potential to mitigate the disease and treatment-related factors of ESRD. Finally, in Section 2.6, the key knowledge gaps in IDE exercise that inform this work are discussed in detail.

In Chapter 3, the results of the first study are presented. In this chapter, the feasibility of two different types of IDE was evaluated using a factorial design and qualitative methods. A version of Chapter 3 is planned for submission to Implementation Science.

In Chapter 4, the qualitative findings from the interviews with trial participants and unit staff on trial implementation are presented. This study has been accepted for publication in the Clinical Journal of the American Society of Nephrology.

In Chapter 5, a study protocol for a realist synthesis is presented. For this study, the data from a systematic review of the literature and interviews with IDE stakeholders will be integrated to explain how contextual factors work to effect varying levels of patient participation in IDE. This protocol has been accepted for publication with Systematic Reviews.

In the final chapter (Chapter 6), the key study findings from each chapter are summarized. How this work contributes to the literature and implications for research and clinical practice is explained. The strengths and limitations of this work are discussed followed by recommendations for future research and policy. The final chapter concludes with the knowledge translation strategy for this work and the overall conclusion to this thesis.

CHAPTER 2-LITERATURE REVIEW

2.1 Brief overview of ESRD

Kidney disease is defined as end-stage when the estimated glomerular filtration rate is less than 15 ml/min/1.73m^2. At this low level of kidney function, the kidneys are unable to excrete adequate fluid and waste, hormonal functions are compromised, and renal replacement therapy either as dialysis or transplantation, is indicated for continued survival. Although transplantation offers the best outcomes, organs are a limited resource and due to advanced age and multimorbidity, many patients are not eligible.[1]

The most common form of RRT in Canada and the United States is conventional HD.[2,3] Conventional HD necessitates four-hour, thrice-weekly treatment sessions typically in a facility or hospital setting. Although HD is a life-sustaining therapy, it confers a significant disease and treatment-related burden. Symptoms that are frequently reported by patients include feeling tired or a lack of energy, itching, depression and anxiety, breathlessness, and pain.[4–6] Common problems experienced during the HD session are restless legs, cramping, and hypotension. Although not explicitly captured by symptom score scales, patients have also identified the time consuming aspect of the HD treatment as interfering with living a 'normal life.'[7] In addition, as time on HD is typically sedentary, with most patients passing the four hours by watching television or sleeping, HD also contributes to the high level of sedentary time in this population.

2.2 Summary of what is known on exercise in kidney disease

2.2.1 An overview of exercise trials over the past 30 years

Prior to the 1980s, patients with ESRD were advised to avoid participation in vigorous physical activities. Clinicians were concerned about the possible development of metabolic acidosis, the effects of hypoxia (induced by anemia), and the consequences associated with the uremia-induced electrolyte derangements.[8] The initial published reports of exercise interventions in this population were aimed at demonstrating that improvements in physiological and biochemical outcomes were possible and well tolerated in highly selected patients. The first trial on exercise in HD patients was conducted in 1983.[9] Twenty-five patients were randomized to either aerobic training 3 to 5 times weekly or a sedentary control for a mean of 12 months. Compared to control, the exercise group showed a 21% improvement in aerobic capacity. Painter et al.[10] conducted the first intradialytic exercise study in 1986. The effect of cycling three times per week over six months versus no exercise in six sedentary controls lead to a similar (23%) improvement in aerobic capacity. Exercise RCTs in people with CKD published in the 1980s and 90s continued to focus on physiological and biochemical outcomes and it wasn't until the early 2000s that interest in the effect of exercise on QoL and physical functioning increased.[11,12] Only over the past ten years has the effects of exercise on dialysis-related symptoms received more attention in the literature.[11,13]

2.2.2 Important considerations in the interpretation of systematic reviews

Overall, RCTs in people with CKD at any stage have typically included less than 70 participants. In addition to small study bias,[14] the challenge for systematic reviews in pooling trials has been the variation in how trial outcomes are measured and the difference in exercise prescriptions among trials e.g. trial durations, setting of delivery, type (aerobic or resistance, or combined), and intensity. Moreover, generalizability of findings has been compromised by strict eligibility criteria.[11,15] Although the number of trials that have included diabetic patients have increased in the past 10 years, trials targeting high-risk groups is still limited. For example, only one study has targeted patients with diabetic CKD.[11]

2.2.3 Overview of findings from systematic reviews and RCTs on exercise in CKD

Current systematic reviews on exercise trials in this population have focused on people with CKD at any stage,[11,12] HD patients,[16–18] and only IDE interventions.[13] (The majority of trials have been performed in HD patients and therefore represent the majority of patients in all reviews.) Across these reviews, the strongest and most consistent data for the benefit of exercise in people with CKD is on aerobic capacity.[11–13,16–18]

Overall, reviews have focused on different outcomes and reported variable effects. A Cochrane review of 45 RCTs (1,863 patients) in people with CKD from 2011 reported that regular exercise improves aerobic capacity, blood pressure, several nutritional parameters, and QoL[12] while Smart et al. reported no effect of exercise on QoL in HD patients.[16] A more recent review of exercise RCTs in people with CKD that included 59 trials (n=2,858), (46 trials were in people on HD) by Barcellos et al.[11] found the most evidence for a benefit of aerobic exercise on aerobic capacity, muscular strength, and quality of life in HD patients. A meta-analysis of RCTs of IDE interventions concluded that IDE improved aerobic capacity, blood pressure, dialysis adequacy, and the physical component of QoL (although the standardized mean difference for the latter three outcomes were small). Interestingly they found no effect on the mental component score of QoL.[13] Only two reviews have included measures of physical performance and small to modest improvements with exercise training were reported.[13,17] No reviews have included dialysis-related symptoms as outcomes.

2.2.4 Aerobic capacity and exercise

Significance of aerobic capacity

Cardiorespiratory fitness (commonly measured as maximal or peak oxygen uptake [$VO_{2\ max}$ or $VO2_{peak}$]) is significantly lower in the ESRD population at 55-65% of age predicted levels for $VO2_{peak}$.[19] As $VO2_{peak}$ reflects the integration of multiple physiological systems, it is a strong predictor of mortality in several populations.[20–22] Sietsema et al.[23] evaluated the relationship between $VO2_{peak}$ and survival in 175 people with ESRD who had participated in separate trials. Those with a $VO2_{peak}$ above the median value of 17.5 ml/kg/min had a 17% lower mortality rate on univariate analysis compared to those with $VO2_{peak}$ below this value over the median follow up of 39 months. In the multivariate model, age and chronic heart failure were the only additional factors that improved its predictive value. However, the analysis was limited by a low event rate and a high risk of residual confounding.

Effects on aerobic capacity

Although the predictive value of $VO2_{peak}$ in people with ESRD has not been clearly established, regular exercise has been shown to improve (although not fully correct) $VO2_{peak}$ to age adjusted norms. In one systematic review of RCTs in HD patients (15 studies, n=565), pooled results from eight studies (n=365) demonstrated a post-exercise training difference in $VO2_{peak}$ of 27.6% (mean difference 5.22 mL O2 /kg per min; 95% CI 3.86, 6.59; P < .00001) compared to control.[16] In the review of IDE interventions (24 studies, 997 patients), Sheng et al.[13] also reported a moderate improvement in $VO2_{peak}$ (SMD 0.53; 95% CI 0.30, 0.76; P<0.001); (seven studies, n=310). Both reviews found greater improvements in $VO2_{peak}$ with longer trial durations. For IDE, combined aerobic and resistance training was associated with a considerable improvement in $VO2_{peak}$ (SMD 0.92; 95% CI 0.53, 1.31) compared to aerobic training alone (SMD 0.32; 95% CI 0.03, 0.60).[13] The Cochrane review also reported a SMD of -0.56 (95% CI -0.70, -0.42) in favor of exercise.[12] Sufficient data was available to identify the most effective exercise prescription to improve aerobic capacity in CKD: four to six months of supervised, regular (three sessions/ week) high intensity mixed cardiovascular and resistance training lasting 30 to 90 minutes.

2.2.5 Quality of life and exercise

Significance of QoL

As discussed in the first Chapter, QoL as a predictor of mortality and hospitalization has been demonstrated across a number of populations with ESRD[24–26] and is viewed by patients as a highly important therapeutic goal.[4,7] Most exercise trials evaluating QoL in CKD have used a generic instrument, commonly the Medical Outcomes Study Short-Form 36 (SF-36).[12,13,27] Studies have used variable domains of this instrument as an outcome: the physical component summary score (PCS) with or without the mental component summary score (MCS), or select subscales (physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health). The effect of exercise on other disease and treatment-related outcomes, such as ability to work, social support, and relevant to IDE, satisfaction with treatment and dialysis staff encouragement have been relatively unexplored.

Effects on QoL

In the Cochrane review, 18 studies included QoL as an outcome, 16 of which were in HD patients. Of these 16 studies, 12 reported significant improvement in at least one of the selected components of QoL.[12] Negative studies in this review generally included higher functioning patients[38] or were underpowered.[28,30] Aerobic exercise was the predominant intervention, study duration ranged from two to twelve months, and a variety of frequencies and intensities of exercise were used. However, two systematic reviews in HD patients (including RCTs from any setting) found no effect on QoL.[16,17] Sheng et al.[13] pooled the results from seven studies (256 patients) of IDE trials and found a beneficial (but small) effect of exercise on PCS score (SMD 0.30; 95% CI 0.05, 0.55). Similarly, the majority of studies evaluated aerobic interventions and only one study compared different types of IDE. Interestingly, IDE did not improve MCS scores (five studies; n=167).

These findings underscore the need for a better understanding of how exercise improves QoL. As regular exercise training has been shown to mainly improve the physical domains of QoL,[12,13] presumably the perception of improved functioning is a result of objective improvements in physiological and physical parameters. Yet, it is not clear why mental domains (e.g., vitality, social role) would not also improve.[13] Furthermore, exercise has been shown to improve symptoms of depression in HD patients. Based on the results from 3 studies in 86 HD patients, the mean difference (MD) on the Beck Depression Inventory, with exercise versus control was −6.9 (95% CI −9.7, −4.1, $p < 0.00001$).[17]

2.2.6 Physical performance and exercise

Significance of physical performance

Physical performance tests are indicators of functional limitations and represent essential actions necessary to function independently.[31] In the general population, performance-based tests of physical function have predicted mortality and disability.[32–34] Few studies have evaluated the association of objective physical performance measures with mortality in people with ESRD, though the most evidence exists for the six minute walk test and gait speed.[35–37]

In a secondary analysis of the large multicenter EXerCise Introduction To Enhance Performance in Dialysis trial (EXCITE), (still in progress), the predictive power of the six minute walk test was evaluated in 296 dialysis patients.[37] Overall, 182 patients had the composite end-point of death/cardiovascular events/hospitalizations. In a bivariate Cox regression model, including the allocation arm as covariate, an increase of 20 meters walked during the 6MWT significantly (P<0.001) reduced the risk of the composite end-point by 6%. Similar results were obtained in bivariate analyses of the individual end-points. In these models, an increase of 20 meters significantly reduced all-cause death by 12% (P<0.001), fatal and non-fatal cardiovascular events by 7% (P<0.001), and all-cause hospitalizations by 4% (P=0.002).

In a separate study, investigators used data from the United States Renal Data System on a prospective cohort of 752 to evaluate the predictive value of gait speed in HD patients.[35] Compared with participants walking ≥0.6 m/s, adjusted mortality hazard ratios were 2.17 (95% CI, 1.19-3.98) for participants who walked <0.6 m/s, and 6.93 (95% CI, 4.01-11.96) for those unable to walk. After 12 months, compared with baseline walk speed ≥ 1.0 m/s (n=169 participants), baseline walk speed of 0.6 to <0.8 m/s (n=116) was associated with increased odds of hospitalization (OR, 2.04; 95% CI, 1.19-3.49) and ADL difficulty (OR, 3.88; 95% CI, 1.46-10.33).[35]

Effects on tests of physical performance

Exercise RCTs in people with ESRD have used various measures of performance-based tests of physical function as outcomes including sit-to-stand, timed up and go, six minute walk test, and the Short Physical Performance Battery.[12,13,15] Trials in HD patients have most commonly used the six-minute walk test and sit-stand tests.[13,17] A pooled analysis of four studies in HD patients (n=129) reported an improvement in six minute walking distance (mean difference of 27.45 meters (95% CI 9.55, 45.34); three of these studies used aerobic exercise.[17] In a pooled analysis of four IDE trials (n= 146) a moderate improvement in six-minute walk distance (SMD 0.58;

95% CI 0.23, 0.93) was reported. A moderate improvement was also shown in 3 trials (n=106) for the effect of exercise on sit to stand in 60 seconds (SMD 0.71; 95% CI 0.31, 1.12). Importantly, although the prognostic value of these tests is clear, the accuracy of physical performance tests in predicting the true clinical effect of exercise interventions is unknown.

2.3 Barriers and facilitators to exercise in people with ESRD

In order to better understand reasons for the low uptake of exercise in this population, several investigators have explored barriers and facilitators to exercise. A range of methods have been used, including surveys,[38–42] individual interviews,[43–45] focus groups[46] or a combination of these methods[47] but the primary focus has been on individual-level factors. Barriers to exercise for patients include: low motivation, fatigue, shortness of breath, pain and depression, no time (attributed to the time consumed by HD), safety concerns about IDE, as well as potential burden of IDE to HD staff.[38,42,45–47] Nephrologists have reported that barriers to recommending exercise to patients in practice include: lack of confidence on how to recommend exercise to patients, concerns about the risks of exercise, and the expectation that patients would not perform exercise.[39] Dialysis unit staff have also reported a lack of confidence in recommending exercise to patients as well as not having time to recommend exercise to patients, and concerns about exercise and equipment safety in the unit.[43,46,48] Patient identified facilitators to exercise include distraction from the boredom of HD, increased sense of well-being, the desire to feel better and attain improved health, support from an exercise professional, approval of a nephrologist, and seeing their peers exercise.[42,44,46,49]

Barriers and facilitators to exercise at the system level have been relatively unexplored. Painter et al.[43] identified a lack of staff training and strategies to support staff in an exercise role and the absence of policies on the incorporation of exercise recommendations into the treatment plan as important contextual factors limiting exercise promotion in the dialysis unit. A consistent finding across several studies has been that although renal health professionals agree that exercise is beneficial for people with ESRD, few recommend it in practice.[39,40,48,50] In one survey that included 142 CKD care providers from a range of professional backgrounds, all respondents acknowledged the importance of physical activity for patients with CKD at all stages, but only 42% of respondents discussed or encouraged it and a minority facilitated implementation on some level.[40] Specifically, only 18% of respondents referred patients to an exercise professional, 12% facilitated provision of equipment for patients to exercise on dialysis on a frequent basis, and 11% reported providing written information about physical activity.

Proposed measures to increase exercise promotion for people with ESRD at the system level have included greater institutional support for exercise by incorporating exercise promotion into practice policies that are tied to reimbursement for dialysis units (in the United States), defining standard roles in the dialysis unit to include exercise promotion, and exercise professional involvement.[43,47]

2.4 The efficacy of exercise interventions in different settings

Several investigators have compared the efficacy of exercise interventions in people with ESRD in different settings (home versus in-center on a non-HD day versus intradialytic delivery). Outcomes have included aerobic capacity, pulse-wave velocity, and physical performance measures. Konstantinidou et al.[51] randomized HD patients to one of three exercise groups or control. The active treatment groups were a 6-month supervised outpatient program consisting of three weekly sessions of aerobic and strengthening training (and swimming and basketball) on non-dialysis days; a supervised intradialytic cycling and lower limb strength program; and an unsupervised aerobic exercise program at a lower intensity, performed at home. The non-HD day group had a higher dropout rate (24%) compared to the IDE group (17%) or the unsupervised group (17%). $VO2_{peak}$ increased by 43% ($p<0.05$) in the non-HD day group versus 24% ($p<0.05$) in the IDE group, and 17% ($p<0.05$) in the unsupervised group. The authors concluded that intense exercise training on non-HD days is the most effective way of training; however, differences in $VO2_{peak}$ (and perhaps adherence) were clearly related to differences in exercise prescription−rather than the influence of setting. Kouidi et al.[52] compared supervised outpatient cycling with intradialytic cycling for three times a week over four years in 48 HD patients. Improvements from baseline in $VO2_{peak}$ were shown in both groups: 70% from baseline in the non-HD day program versus 50% from baseline in the IDE group at one year. Similarly, the non-HD group had higher drop out. Koh et al.[28] randomized 70 HD patients to either 6 months of supervised IDE or a home-based walking program (to achieve the same volume of exercise as the IDE group) or to usual care. There were no significant differences between groups in the primary outcome of 6-minute walk test distance (IDE, +14%; home-based exercise, +11%; usual care, +5%) or pulse wave velocity. Adherence to sessions was similar between groups, although the adherence data in the home group was collected by diary and therefore may have been less accurate than that for the IDE group. Unfortunately, like other exercise studies in this population, adherence to the exercise protocol i.e., how much work was actually performed by each group is not known and therefore conclusions about the influence of exercise setting on effectiveness is limited.

Based on the studies discussed above, any form of regular exercise appears to improve aerobic capacity. The findings also suggest that there is an association between IDE and improved adherence to exercise. The association between IDE and increased adherence supports what was discussed above from qualitative studies. That is, exercise during dialysis time has the potential to mitigate HD–related barriers (post-HD fatigue, no time for exercise) and may be facilitated by seeing their peers exercise and obtaining nephrologist approval.

2.5 Rationale for intradialytic exercise

Aside from the potential to improve exercise adherence, there are other compelling reasons to implement exercise during dialysis time. Importantly, IDE may improve a number of disease and treatment-related factors. For example, exercise is a non-pharmacological treatment for restless legs syndrome (RLS). RLS affects approximately one out of three ESRD patients[53] and has been associated with insomnia, decreased quality of life, increased morbidity and mortality.[54–56] Symptoms of RLS during HD are also independently associated with premature discontinuation of dialysis.[57] Four small RCTs have reported that regular, low-moderate intensity cycling during HD can improve symptoms by 28-58%.[58–61]

IDE has been shown to improve dialysis adequacy. Based on six RCTs (233 patients), Sheng et al.[13] reported a small improvement in dialysis adequacy as measured by Kt/V (SMD=0.27, 95% CI 0.30-0.76). Most trials evaluated thrice weekly intradialytic cycling at low to moderate intensity. Only one RCT evaluated the effect of resistance training on Kt/V and showed no effect.[62]

IDE is also one potential means of improving patients' low satisfaction with HD care.[63] In qualitative studies, patients have reported decreased boredom during the HD shift, a sense of enhanced well-being, and a sense of greater involvement in their own care after participating in an IDE program.[44,45] Furthermore, given that the age and comorbidity burden of the average HD patient is increasing, it is important for renal care providers to recognize how this influences nephrology practice. What has been known as a fast paced, technologically focused specialty is now increasingly confronted by geriatric issues e.g., frailty and physical impairment.[64] The role of dialysis in worsening physical impairment was demonstrated by Tamura et al.[65] In this observational study of 3,702 nursing home residents, independent of age, sex, race, and functional-status trajectory before the initiation of dialysis, HD initiation was associated with a marked and sustained decrease in functional status. Aside from our ethical obligations to attend to this problem and from a practical perspective, a more functionally dependent population places increased demands on dialysis providers and has direct implications for how care is provided.[66,67] In this context, it becomes increasingly important to offer therapeutic interventions to improve QoL and functional status, such as exercise. Yet–and in contrast to other chronic diseases, renal exercise programs are scarce. Although the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines offer the recommendation that ‘‘all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" (guideline 14.2),[68] beyond patient referral to other disciplines for exercise and rehabilitation, our role in facilitating exercise is undefined.

2.6 Knowledge gaps in intradialytic exercise

This thesis investigates the key knowledge gaps influencing the uptake of exercise into nephrology practice. How these questions are investigated in this thesis is shown in Figure 2-1. Several of these gaps identified below are relevant for chronic kidney disease at any stage, while others are specific to IDE.

2.6.1 How do we optimize the exercise prescription to improve outcomes in people with CKD?

The components of the exercise prescription are frequency, intensity, type, and time, known as the FITT principle. Each component of the prescription can be manipulated in order to target a training-specific outcome. However, few exercise studies in people with CKD have compared different exercise prescriptions. One recommendation from the 2011 Cochrane review was that more RCTs evaluating different types of exercise, specifically resistance and aerobic combined or resistance alone were needed.[12] Since the date of the authors' last search (March 2010), 55 RCTs on exercise in people with CKD have been published (Medline, EMBASE, Cochrane Central Register of Controlled Trials [CENTRAL]); (Search strategy and results are shown in Appendices 1 and 2). Of these RCTs, resistance interventions represent only nine studies and combined interventions only six while aerobic interventions still predominate, accounting for 34 studies. Only four studies have compared aerobic and resistance exercise and only two studies evaluated other types of exercise. Based on this search, no RCTs compared how altering other components of the exercise prescription (e.g. intensity) may influence outcomes.

In contrast to the renal exercise literature, trials comparing different exercise prescriptions in other populations are more comprehensive.[69–74] A systematic review comparing different exercise protocols in people with chronic obstructive pulmonary disease (COPD) found that resistance training was associated with greater improvements in health-related quality of life than endurance exercise (weighted mean difference 0.27, 95% confidence interval 0.02, 0.52).[69] Differential effects of different types of exercise on QoL and disease symptoms have also been described in people with prostate cancer,[75] as well as in the elderly.[76] Courneya et al.[74] evaluated a type and dose effect of exercise in women undergoing chemotherapy for breast cancer. A standard dose of 25 to 30 minutes of aerobic exercise did not confer any additional benefit compared to a higher dose of 50 to 60 minutes of aerobic exercise or a combined dose of 50 to

60 minutes of combined aerobic and resistance exercise for the primary outcome of physical functioning.[74] A systematic review in people with heart failure evaluating different intensities of the exercise prescription reported that irrespective of baseline fitness or exercise volume, cardiorespiratory fitness (measured as peak Vo2) improved by 23% from baseline with high intensity training compared to a weighted mean percent change of 13% in the moderate intensity group.[73] Importantly, higher intensity exercise was not associated with lower adherence or higher adverse events (AEs).

As shown by the above examples, the question of what to prescribe for exercise is not simply an academic concern. Clear messaging to health providers on what to recommend to patients for the optimal exercise prescription—what to do to most effectively achieve the desired outcome while minimizing risk, is critical to increasing patient participation and adherence. In people with heart failure, specific advice in the form of an exercise prescription or goal setting increases adherence to exercise.[77] Furthermore, physicians have an influential role in supporting behavior change[78–80] but often lack confidence on how to recommend exercise to patients.[39]

2.6.2 What are the specific safety concerns with exercise in people with CKD?

Although there have been no serious adverse events reported in the CKD exercise literature,[17] safety remains an important concern for nephrologists[39] and is a recognized barrier to the participation in and uptake of IDE for patients and dialysis unit staff.[47,81] Despite this knowledge, the reporting of adverse events in these trials is not rigorous. For example, only one of the 45 studies included in the Cochrane review[12] included adverse events as an outcome.[82] The review by Sheng et al.[13] did not find an increase in musculoskeletal and cardiovascular complications with IDE versus control, but only three studies were included in the meta-analysis and none of the remaining 21 studies included AEs as an outcome, which raises the concern that events are under-reported.

Cardiology has faced similar challenges to the adoption of exercise into practice for people with heart failure with reduced ejection fraction. Prior to the large multicentre trial, Heart Failure-A Controlled Trial Investigating Outcomes of exercise TraiNing (HF-ACTION) in 2009,[83] there were numerous RCTs on exercise in this population;[84] however, limited sample sizes and the lack of definitive data on clinical outcomes and safety were cited as barriers to its adoption in clinical practice and was also cited as a reason why this diagnosis was not insurable for cardiac rehabilitation in the United States.[85] HF-ACTION was a multicenter, randomized controlled trial that enrolled 2,331 medically stable outpatients with heart failure and reduced ejection fraction. The aim was to evaluate whether aerobic-type exercise training reduced the primary composite end point of all-cause mortality or all-cause hospitalization and secondary end points of all-cause mortality, a composite of cardiovascular mortality or cardiovascular hospitalization, and the composite of cardiovascular mortality or heart failure hospitalization. Other cardiovascular adverse events included worsening heart failure, myocardial infarction, unstable angina, serious adverse arrhythmia, stroke, and transient ischemic attack, hospitalizations due to fracture, cardioverter-defibrillator (ICD) firing events (for subjects with an ICD), and all hospitalizations occurring within a defined period of exercise training. Although viewed by some as disappointing with only a non-significant 7% reduction in all-cause mortality and hospitalization in the primary unadjusted analysis, the safety of moderate intensity exercise training in this population was clearly shown. The results from this trial have been regarded as influential in obtaining the eventual approval from Medicare and Medicaid to reimburse cardiac rehabilitation for people with heart failure with reduced ejection fraction.[85]

This discussion of the HF-ACTION trial is not intended to imply that a trial this large or resource intensive is necessary in order to change practice. It is however, meant to highlight several important issues for the design and reporting of exercise trials in people with ESRD. First, formal evaluation of AEs adds credibility and accuracy to event detection. Second, safety outcomes should include those relevant to patients and providers. The potential for vascular access compromise during IDE has been reported in the IDE literature[47,86] yet, the risk of this AE has only been systematically evaluated in one IDE trial.[62] In addition, given the high prevalence of diabetes in the ESRD population, certain types of events such as hypoglycemia, may occur more frequently with exercise. Knowledge of these events would inform discussions between patients and clinicians on the relative benefits and risks of different exercise programs and potentially improve the clinician confidence in recommending exercise to patients.

2.6.3 How do we address known limitations in IDE trial design?

While there are numerous pilot studies evaluating IDE, these are primarily small-scale efficacy studies that have not addressed feasibility. This gap in the literature is surprising given known methodological limitations of existing trials and the complexity of IDE delivery. Small-scale studies that rigorously evaluate the methodological and practical issues in IDE trial design and delivery are a valuable tool for improving the quality of future trials.

Methodological issues in IDE trial design

Several of the key methodological issues that have been identified in systematic reviews of exercise trials in people with chronic kidney disease are: the limited use of allocation concealment, blinded outcome assessment, and intention to treat analysis.[11,12,16] Of the 45 randomized control trials that were included in the Cochrane review, the overall risk of bias was high in 49% and moderate in 33% of studies.[12] In their review of exercise interventions in HD patients, Smart et al.[16] reported a median Jadad score of 2 (low) for trial quality, primarily due to unclear information on blinding. Sheng et al.[13] reported overall quality of IDE trials was moderate; however, only five of the 24 included trials used blinded outcome assessment. Although these limitations are problematic for the interpretation of study findings, how to fix these design issues in future studies is straightforward. Conversely, blinding participants and providers to treatment allocation in non-pharmacological interventions such as exercise, is more challenging. This issue is highly relevant to IDE, where the intervention is often delivered in the open setting of the dialysis unit among other trial participants and dialysis unit staff. For non-pharmacological, participative interventions such as IDE, there are several methods that can be used to blind participants and/or providers: attention control interventions of a same or a different type, and blinding to study hypothesis.[87] An understanding of the utility and practicality of these methods in mitigating the consequences of unblinding e.g., attrition bias, contamination, and differential administration of co-interventions, would be useful information for the design of future studies, but have not been evaluated in the IDE literature.

Practical issues in IDE trial design

There is limited data on how the setting, processes, and the characteristics of the intervention influence the effectiveness of IDE. The majority of IDE trials have focused exclusively on demonstrating the intervention's efficacy (the performance of the intervention under ideal and controlled circumstances) to the exclusion of external factors (i.e. everything aside from the exercise alone). Given that the context of IDE trial implementation is complex with differences in resources, expertise, and organizational readiness for IDE, this narrow approach to evaluating IDE interventions is inadequate. First, the setting of the dialysis unit is a busy and often resource limited setting that is structured to deliver HD—not exercise. Therefore, how IDE is implemented into the workflow and environment of the dialysis could influence the integrity of trial implementation. Second, as the HD session is time that is typically devoted to sedentary activities such as watching television or sleeping, social norms about what behaviors are expected by unit staff and patients during the dialysis treatment could influence intervention adherence and sustainability. Third, people with ESRD tend to be inactive, with physical activity levels below the fifth percentile of the general population[88] but how program characteristics could promote acceptability and adherence to exercise in this population has not been explored. Fourth, experts recommend the involvement of exercise professionals in IDE program delivery; yet, aside from the technical aspects of their role, their effect on IDE delivery has not been described.[89,90] Lastly, dialysis unit staff have frequent contact with HD patients, often over a long period of time and to what degree unit staff perceptions influence patient decision making and trial implementation is unknown.

2.6.4 How do we increase the impact of IDE trials?

For the purposes of this discussion, research impact is defined as the relevance to research users and the benefits to patients and renal organizations in terms of increased adoption and sustainability of IDE in practice.[91,92] For research users, decisions on the relevance of an intervention are often based on what is known about its effectiveness and its transferability (the extent to which users of evidence can apply the results from one context to another). To assess the transferability of the evidence, information is needed on the intervention, context, and the interactions between these.[93] This type of evidence is often not included in traditional appraisal criteria[93,94] and is not adequately provided in IDE studies.

To facilitate the uptake of exercise into nephrology practice, evidence-based strategies for a well-operationalized program are needed. This includes information on the key components and unintended consequences of IDE. Key components are those essential parts of an intervention that have an effect on outcomes but are distinct from the intervention's mechanism of action. These components can define an effective program and should be maintained as the program is adapted to different contexts.[95,96] Unintended consequences are the unpredicted effects of the intervention, which may be positive and add to the intervention's value, or negative, and require adjustment prior to scaling up. Qualitative methods are especially useful for understanding these aspects of an intervention but have not been used alongside randomized trials in IDE.[97]

2.6.5 How do we inform the adoption of IDE in clinical practice?

The uptake of research findings into clinical practice is often slow or nonexistent.[98] Reasons for slow uptake have been discussed in the literature;[99] however, one under-recognized factor is the research user's inability to carry out the treatment based on the limited information provided in the published report.[100] In a review of 80 published reports of treatment interventions from high impact clinical journals, elements of the intervention were missing for approximately half of the published descriptions. Notably, information was more complete for pharmacological interventions that for non-pharmacological interventions and a description of the processes associated with delivering the intervention was commonly omitted.[100] Information on context and process is of particular importance to complex and potentially resource intensive interventions like IDE, but are missing from trial descriptions. This information is not only necessary to increase research use, but also to understand the inconsistent effects of exercise interventions reported in the literature specifically, those on QoL.[11–13,16,17] These differences could be explained by variation in important contextual factors. The potentially relevant contextual factors for IDE programs include individuals (the skills, knowledge, and involvement of those delivering the program); interpersonal relations (the lines of communication among staff and through different organizational levels); institutional factors (job descriptions or policies that incorporate aspects of the program); and resources (funding, space, equipment, and incentives).

To increase IDE uptake, research users need to know more than just if the intervention is effective, but also what type of program to put resources into i.e., what type of skill development, personnel, or policies is needed to make the chances of program success more likely. Therefore, the limitations of RCTs in providing this type of evidence is not simply a reporting issue, but rather a matter of study design. RCTs aim to answer the question of whether the intervention works (i.e. *does the intervention work on outcome X?)* and not the question of how a program achieves its effects (i.e. *how does the intervention work to bring about its intended outcome?)* To appropriately answer the latter, theory-based approaches that aim to understand contextual influences on why and how interventions might work are needed.

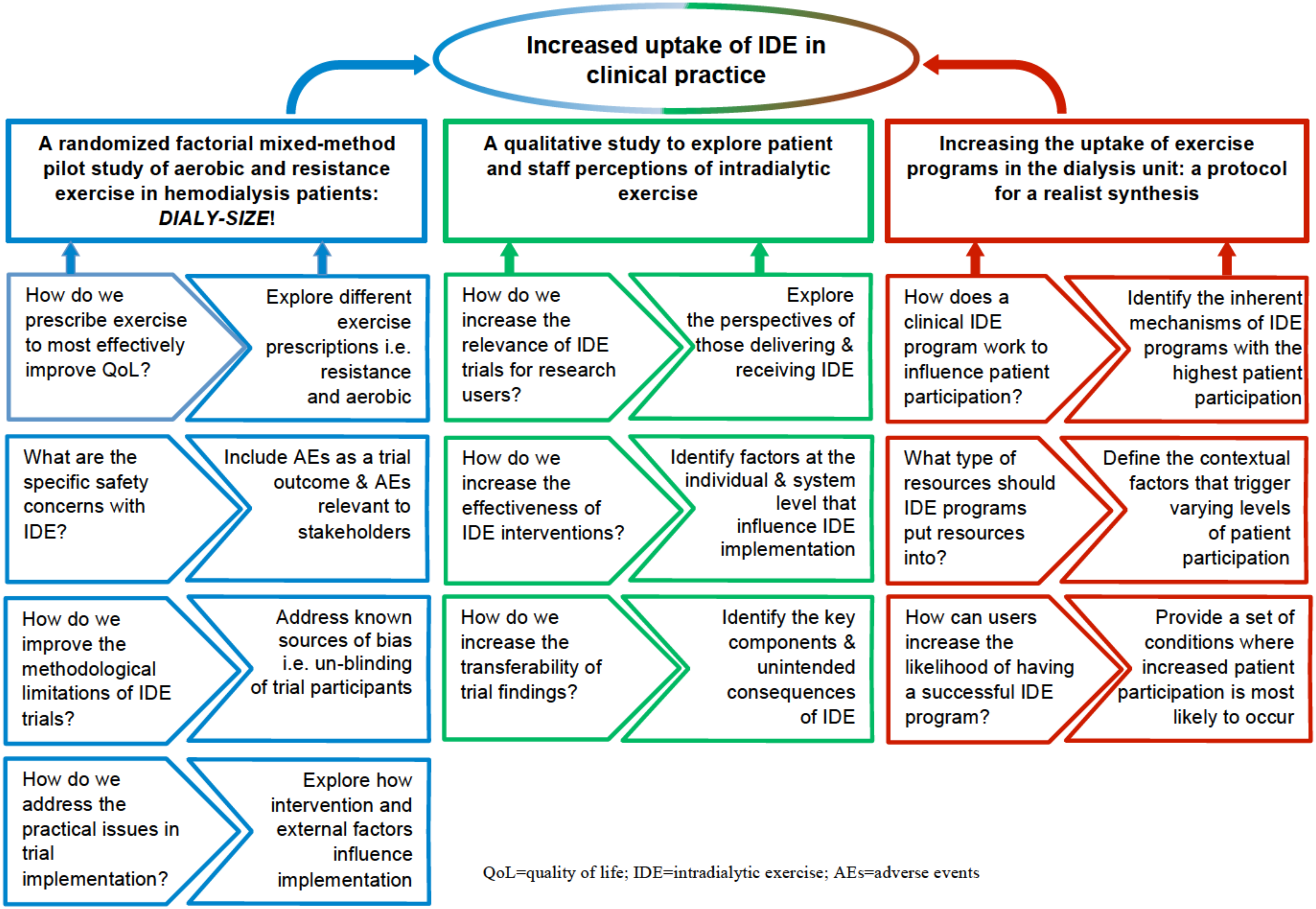
The realist line of inquiry is a theory-based approach, rooted in critical realist philosophy[101] that focuses on causal mechanisms (processes or structures that trigger a behavior) to explain how interventions work (or don't work) according to specific contextual factors.[102] The overall aim of the realist approach is to explain what and how contextual factors increase program effectiveness and make recommendations as to how this can be generalized across different programs.[103] Realist synthesis is an increasingly popular approach to knowledge synthesis.[104] The strength of the realist line of inquiry is that diverse sources of both qualitative and quantitative data can be used, a structure for understanding the complexity of real world implementation is provided, and that in order to go beyond a "one size fits all" approach to problem solving, there is an emphasis is on engaging research users and stakeholders.[103]

2.7 Conclusions

The efficacy of exercise in improving aerobic capacity in people with ESRD is consistent across a number of systematic reviews and there is accumulating evidence to show the benefit of exercise on measures of physical performance. Several systematic reviews have reported a positive effect of exercise on QoL while in pooled analyses, other reviews have reported a no effect or a small effect. Explanations for this variability include varied exercise prescriptions and contextual factors, and heterogeneous study populations.

Although renal health professionals have recognized the benefits of exercise in people with ESRD and there is a strong rationale for including IDE in HD care, few report facilitating implementation in practice. In the literature, this disconnect has been attributed to low patient motivation to engage in exercise and multimorbidity, renal health care provider's limited knowledge on how to recommend exercise to patients, concerns about the safety of exercise, and the lack of infrastructure at the institutional level to assist care providers in promoting exercise. The significance of these barriers are made evident by the variable uptake of IDE programs and the lack of exercise-specific guidelines or a definitive position statement from K/DOQI on the priority of exercise in the care of renal patients.' These barriers are in-keeping with the knowledge gaps presented in section 2.6. Clear evidence-based messages to health providers on what to recommend to patients to achieve the desired outcome without increasing the risk of AEs could improve exercise counseling and inform evidence-based guidelines for people with ESRD. Broadening the evaluation of barriers from unmodifiable patient factors to include the system level factors that influence patient participation would provide research users with strategies on how to successfully operationalize exercise within the busy setting of the dialysis unit. Furthermore, perspectives on the effectiveness of exercise may be influenced by renalism. This view could be challenged by increasing the impact of the exercise literature e.g. a more rigorous approach to reducing sources of bias, greater exploration of outcomes relevant to patients (i.e. decreasing the disease and treatment-related burden of ESRD), and by optimizing aspects of the setting and processes of IDE delivery.

Figure 2-1. Knowledge gaps investigated in this thesis and how they will be evaluated.



QoL=quality of life; IDE=intradialytic exercise; AEs=adverse events

CHAPTER 3

A RANDOMIZED FACTORIAL MIXED-METHOD PILOT STUDY OF AEROBIC AND RESISTANCE EXERCISE IN HEMODIALYSIS PATIENTS: *DIALY-SIZE*!

3.1 Abstract

Introduction

End-stage renal disease (ESRD) requiring hemodialysis is associated with low quality of life and a high degree of functional impairment. Routine exercise can improve both of these outcomes although how to optimize the exercise prescription in this population is unknown. We designed a trial to compare the efficacy of two different types of exercise (cycling and resistance) each performed during the hemodialysis treatment. Prior to proceeding with a more definitive study, more information is needed on feasibility, including the practical challenges of implementing an intradialytic exercise program.

Methods

In this single center, randomized, factorial (2 x 2) pilot trial, hemodialysis patients were randomized to one of four exercise groups: cycling, resistance, cycling and resistance, or stretching (an attention control). Feasibility was defined a priori by criteria on recruitment, fidelity to the protocol, and participant response to the intervention. To better understand threats to 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 quality of life, physical function, and strength.

Results

We exceeded the target accrual of 28 subjects over 12 weeks, demonstrating recruitment feasibility. Irrespective of exercise group allocation, adherence was high: of the 1,038 training sessions offered, 87% were initiated, and > 80% of exercise sessions were performed as per protocol. Progression based on perceived exertion, individual instruction, and the support of the kinesiologist facilitated acceptability across all exercise groups. Measures of contamination and attrition due to unblinding of group allocation 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 appears feasible with minor modifications. In addition to practical assistance, involvement from unit staff could increase patient participation and intervention sustainability. Strategies to increase acceptability of the intervention for unit staff include improving workflow integration and using a pre-study demonstration phase to introduce the intervention.

Trial registration: ClinicalTrials.gov NCT02234232

3.2 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 with attendant impairment in the ability to perform the physical tasks of daily life. [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 many activities of daily living 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 our 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] In addition, the evaluation of non-pharmacological interventions, such as exercise have well-recognized design limitations, such as lack of blinding to treatment assignment[4,12] and the evaluation of practical approaches to improve this is of use to research users.

3.3 Methods

3.3.1 Study design

In this mixed-methods study comprised 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 health-related quality of life, physical function, and strength. The two factors evaluated were aerobic exercise (cycling) and resistance exercise (weights). The rationale for using a factorial design is for the efficiency of testing more than one intervention in the same participants. (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). Chronic, adult, in-center hemodialysis 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.

3.3.2 Setting and participants

Recruitment and the intervention took place in a quaternary 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]

3.3.3 Randomization and blinding

Participants were randomized to one of the four exercise groups 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. 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. 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.

3.3.4 Exercise intervention

Participants exercised at each thrice-weekly dialysis session over 12-weeks (36 sessions). The exercises were completed during the first three hours of the four-hour dialysis session. A kinesiologist instructed participants on how to perform all exercises and was present for approximately two to three of the participants' thrice weekly dialysis 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).[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 training session started and ended with a five-minute warm-up and cool-down on the cycle ergometer at an intensity of 9-11 (very light to fairly light on the Borg scale). The progressive cycling protocol started with 15 minutes of cycling with time increased by 2.5 minutes each week. The intensity of the exercise was adjusted to maintain the target RPE of 12-14. 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

The resistance group performed four types of exercises targeting the lower limbs: three different leg exercises were performed with the ankle weights (Fabrication Enterprises, White Plains, NY): knee extension, knee flexion, and hip flexion. A Theraband (The Hygenic Corporation, Akron, OH) was used for hip abduction. Patients warmed-up by performing one set of all exercises against gravity. The resistance protocol progressed from one set of 10-15 repetitions for each exercise to three sets. When the patient's RPE for that exercise was less than target for all 3 sets, the amount of weight (or the resistance of the band) was increased.

Combined intervention

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

Attention control

To equalize the effect of co-interventions,[15] the control group was assigned a non-progressive stretching routine during dialysis. Participants performed 2 sets each of four exercises for the lower limbs and core muscles: 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. The kinesiologist supervised the stretching program.

3.3.5 Data collection

Demographic and 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 exercise session, the following data were 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 a review of the HD chart.

3.3.6 Primary outcomes

The primary outcome of feasibility was defined by a priori criteria (Table 3-2) 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 for both patients and dialysis unit staff).

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 (36-session) 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 3-2).

Response to the intervention

Acceptability of the exercises was defined as ≥50% of participants reporting that they would like to continue their current intradialytic exercise 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.

3.3.7 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 members 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 after their 12-week study participation. All RCT participants were eligible to participate if they were capable of sharing their experiences. Interviews were semi-structured and included open-ended questions followed by more 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 (recruitment, fidelity to the protocol, and impact of the intervention on patients and staff) and analyzed to yield a descriptive summary of study findings.

3.4 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 adverse events (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) is an objective performance-based measure for the lower extremities that 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 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 adverse events compared the frequency of events during the exercise session compared to control, by randomization group. In a sensitivity analysis, all events occurring during the 12-week intervention period were analyzed. In both analyses, only the first event per individual was counted (for each type of adverse event).

3.5 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. Analysis of covariance (ANCOVA) was used to adjust for the baseline score and the other intervention (main effect term).[27] 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 study's primary outcomes.[28] 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).

3.6 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 3-1). 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) (Table 3-1). The primary cause of ESRD was glomerulonephritis (32.3%) followed by diabetes (22.6%). Forty-eight percent of participants were diabetic, 90% had hypertension, 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 mean age of patient interview participants was 59 years (SD 14.4); 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.

3.7 Feasibility

Feasibility outcomes are shown in Table 3-2. To highlight key themes regarding the trial's feasibility, exemplar quotes from the interviews of staff members and patients are shown below.

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.

"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"

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. Several staff also expressed concern that the exercise equipment would have a negative impact on their workspace.

"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."

<u>Dialysis unit staff (pre-trial interviews): selection of suitable candidates</u>

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.

"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..."

Staff also discussed factors that could influence 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.

"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."

<u>Modifications to the trial protocol</u>

Based on the interview findings, instead of a didactic in-service, two practical in services were held to focus on study procedures and equipment set-up. Education materials, including copies of key studies on IDE and pamphlets on study procedures were available on the unit. In response to suggestions from unit staff, a video giving a brief overview of the exercises as well as how to assist patients with equipment set-up and complete documentation was posted on YouTube (www.youtube.com). To address concerns regarding patient safety and hemodynamic stability during IDE, prior to enrolling a patient, the charge nurse was consulted regarding any dialysis-related safety concerns. We were not successful in engaging any unit staff to volunteer as "exercise champions" to identify issues with implementation and liaise between HD and study staff. As an alternative, we identified four unit staff that had taken leadership roles in the unit in the past to act in a similar, but more informal role. We carried-out regular check-ins with these exercise 'point people' throughout the trial.

<u>RCT participants: recruitment</u>

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.

"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.

<u>Dialysis unit staff (mid-trial interviews): fidelity to the protocol</u>

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 unit staff reported that there were technical challenges with retrieving HR and BP data for the exercise DCFs from the HD machines. Some staff also mentioned that recording the vital signs was too time consuming.

"...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."

One commonly discussed barrier to the staff's involvement in the trial was not having enough staff and there being "no time"[21] 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 workload on the unit had a negative influence on 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.

"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!"

<u>*RCT participants: fidelity to the protocol*</u>

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 group for > 80% of exercise sessions (Table 3-2). Exercise parameters are shown in Table 3-3 including mean volume of exercise performed in the active intervention groups. For the active intervention groups, the mean RPE was within the targeted intensity range. In the active intervention groups, 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. Individualized instruction, progression based on perceived level of difficulty, and support from the kinesiologist[21] were commonly mentioned as strengths to the exercise program. Several patients also expressed that knowing there was the expectation of having to exercise facilitated adherence.

"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..."

Of the 1,038 exercise sessions that were offered, only three were terminated early. Two sessions were stopped in the cycling group, one due to consistently elevated blood pressure and one due to discomfort from poor positioning with the bike. One patient in the combined group terminated cycling early due to fatigue. 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. Hemodialysis-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.[21] 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, unit staff participants agreed that the exercise program was valuable for patients. 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.

"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…"

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).[21]

RCT participants: impact of the intervention

Across all exercise groups, the patients' responses to exercise was highly favorable: 92% of participants reported they wanted to continue IDE after the trial and 63% wanted to continue exercising with their current regimen. All patients in the combined group wanted to continue with cycling and weights whereas most patients in the stretching group expressed interest in either cycling or weights (Table 3-2). There were no crossovers during the trial. We did not detect a change in the amount of physical activity or amount of exercise performed outside of the unit during the trial. 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 the exercises 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 component of an exercise regime. One participant commented that due to a shorter exercise routine, interaction time with the kinesiologist was relatively brief.

"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..."

Patients commonly discussed the benefits of IDE and for many, these results were what motivated them to continue exercising. Patients discussed the exercise-related benefits of IDE, such as greater strength and endurance and several patients attributed improvements in daily functioning to participation in IDE. Improvements in their dialysis-related symptoms were also mentioned, primarily decreased cramping and restless legs.

"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..."

The most common benefit of IDE that was mentioned was that it *"helped kill the four hours"* and that it made the time on dialysis more enjoyable. For one participant, distraction during dialysis was highly significant as it served as an escape from HD.

"Like an escape from the humdrum. Because like I said, the entire dialysis thing is a very stressful thing, both physically and mentally... you start doing that communication with someone on a different subject or something that's totally unrelated to your normal health problems or the problems that you're going through life-wise, and concentrating on the exercise or something different, and it's an escape or whatever from the dreariness of the situation you really find yourself in..."

<u>*Adverse events*</u>

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 3-2. 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 3-3). 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.

3.8 Secondary outcomes

The absolute differences in scores for secondary outcomes are shown in Table 3-4. 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).[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.

3.9 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, high patient acceptability, and a low risk of contamination and attrition due to unblinding of group allocation. 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 IDE and clinical program implementation: 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. 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.[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, 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.[21] Third, given that many patients experienced difficulty consistently obtaining exercise equipment from unit staff has clear implications for patient adherence.[21]

To allow for greater integration in the unit's workflow, several study procedures will be modified. The amount of time required for exercise data collection was not acceptable and resulted in missing data. This issue was recognized early in the trial and resolved with greater involvement from study staff; however, this strategy is not feasible for a multisite study. After reviewing the pilot data, we consider vital signs collected pre, post, and peak exercise as sufficient for exercise data collection for the main study. 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 dialysis 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, 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.[40] Our protocol specified that patients finish their exercise within the first three hours of the dialysis shift. Our blood pressure and safety data supports the safety of this approach; however, 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.[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. 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. Finally, 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[43] 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.

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.

Figure 3-1. Randomized controlled trial participant flow

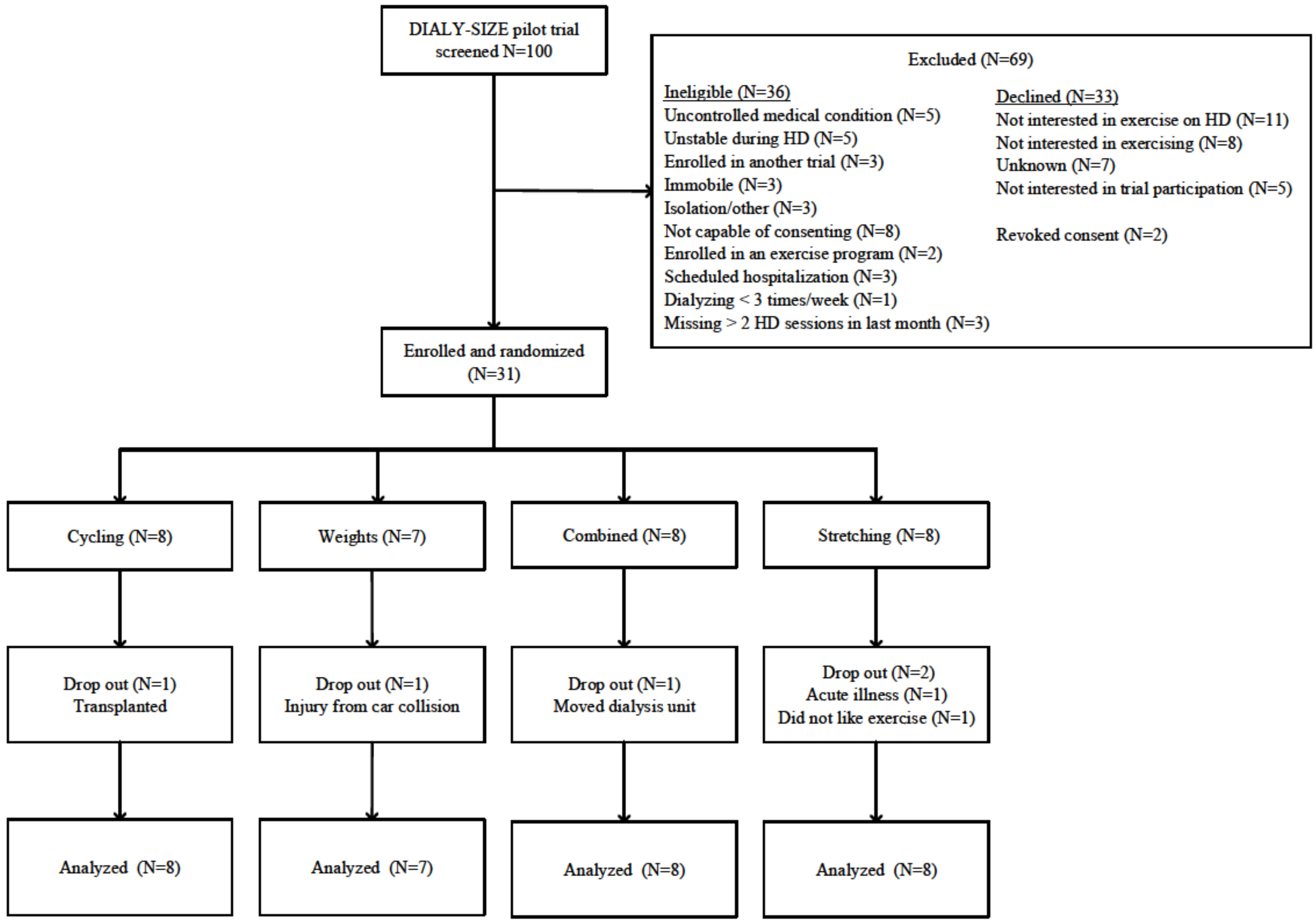


Table 3-1. Baseline characteristics of trial participants

	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	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	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 3-2. 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

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 3-3. 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 3-4. 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 versus no cycling -0.076 (-5.9, 5.8); P=0.979		Weights versus 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 versus no cycling 0.23 (-6.0, 6.5); P=0.94		Weights versus 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 versus no cycling 1.7 (0.2, 3.3) P=0.028		Weights versus 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 versus no cycling 12.8 (-36.1, 61.6) P=0.60		Weights versus 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 versus no cycling -0.31 (-2.7, 2.1) P=0.79		Weights versus 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 versus no cycling -3.4 (-11.0, 4.2) P=0.37		Weights versus 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 3-2. Adverse events occurring during the exercise session

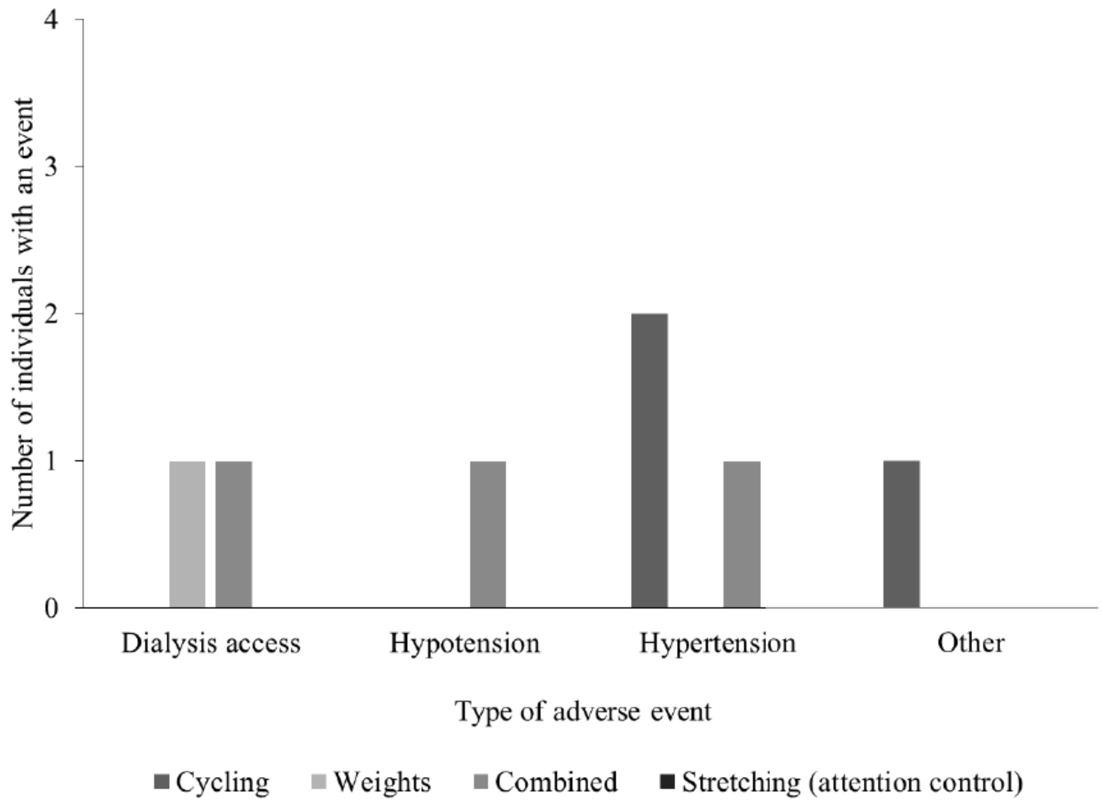
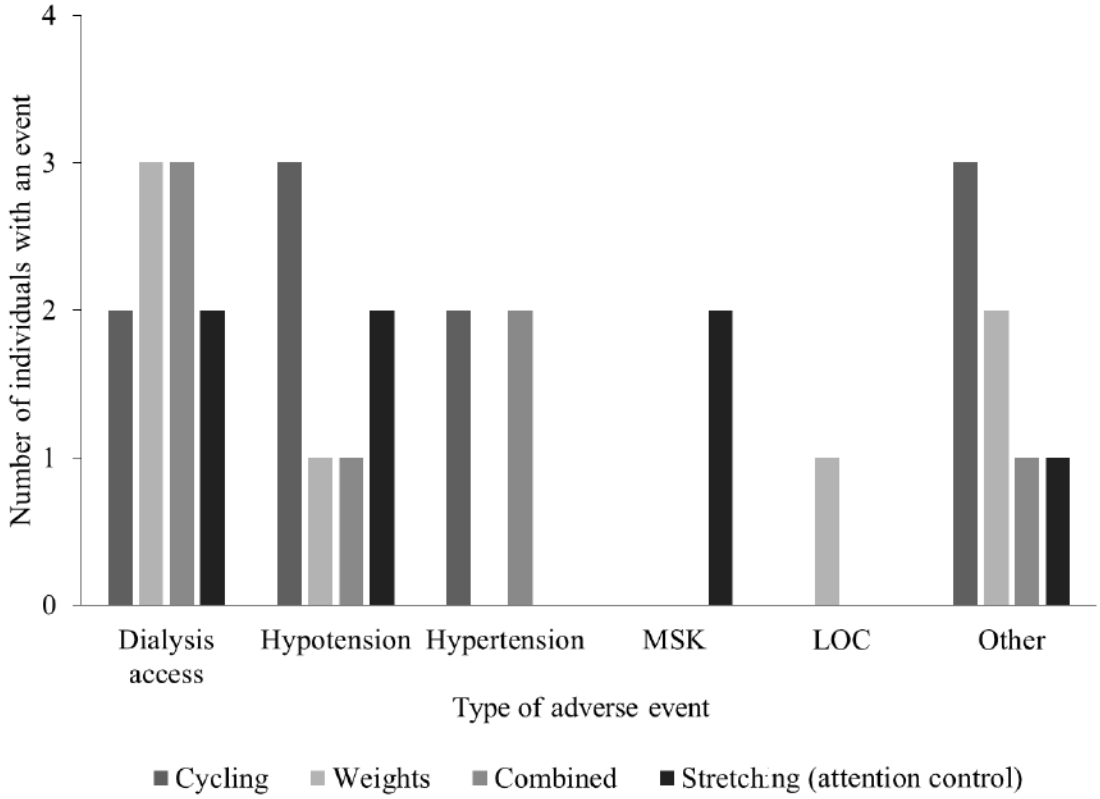


Figure 3-3. Adverse events occurring over the study period



CHAPTER 4

A QUALITATIVE STUDY TO EXPLORE PATIENT AND STAFF PERCEPTIONS OF INTRADIALYTIC EXERCISE

4.1 Abstract

Background

Randomized controlled trials (RCTs) show that regular exercise is beneficial for hemodialysis patients. Intradialytic exercise (IDE) may have additional benefits, such as amelioration of treatment-related symptoms. However, the factors that influence the implementation of IDE are largely unknown.

Methods

Individual, semi-structured interviews were conducted with a purposive sample of hemodialysis patients who had participated in a pilot RCT on IDE and with dialysis staff that worked in the unit during the trial. The trial took place from July-December 2014 and enrolled 31 patients. Interviews were conducted from April-December 2014. Interview coding followed an inductive and broad-based approach. Thematic analysis was used to group codes into common themes, first individually and then across staff and patient interviews.

Results

Twenty-five patients and 11 staff were interviewed. Three themes common to both groups emerged: support, norms (expected practices) within the dialysis unit, and the role of the dialysis nurse. The support of the kinesiologist enhanced patients' confidence and sense of capability and was a key component of implementation. However, the practice of initiating exercise at the start

of the shift was a barrier to staff participation. Staff focused on the technical aspects of their role in IDE while patients viewed encouragement and assistance with IDE as the staff's role. An additional theme of "no time" (for staff to participate in IDE) was influenced by its low priority in their workflow the demands of the unit. The staff's emphasis on patients setting-up their own equipment and enhanced social interaction among participants were additional themes that conveyed the unintended consequences of the intervention.

Conclusions

The kinesiologist-patient interactions and staff readiness for IDE were important factors in the implementation of IDE. Understanding how unit workflow and the personal values of staff can influence implementation may improve the design of IDE interventions.

4.2 Introduction

Hemodialysis (HD) treatment is characterized by low quality of life (QoL), comparable to people with metastatic cancer.[1] The association between QoL, mortality and hospitalization has been shown in end-stage renal disease (ESRD)[2–4] and reducing the physical, social, and psychological impact of kidney disease is a top research priority for people with ESRD.[5]

Randomized controlled trials (RCTs) in people with ESRD show that regular exercise can improve QoL[6–8] by targeting physical functioning.[9] Exercise prescribed during dialysis (intradialytic exercise, [IDE]) may ameliorate treatment-related symptoms (such as restless legs),[10] improve patients' experience of the dialysis treatment[11] and is regarded as safe.[12] Given the paucity of other interventions that improve QoL in this population,[13] it is unclear why IDE remains underutilized.

Previous qualitative studies in people with ESRD have identified post-HD fatigue and low motivation [14,15] as barriers to exercise participation. However, few studies have explored the perspectives of dialysis staff[15,16]or the contextual factors that influence IDE uptake.[17] Understanding the perspectives of both those delivering and receiving IDE can improve the design and implementation of interventions.[18] Further, the context of IDE implementation is complex with variable resources, expertise, and organizational readiness for IDE; what may facilitate implementation in one setting may not work in another. To develop more effective IDE interventions, detailed information is needed on the intervention, the context of the dialysis unit, and the interaction between these factors.[19] These aspects of IDE may be difficult to identify with quantitative methods alone.

In this qualitative interpretive descriptive study, we conducted interviews with participants of a pilot RCT on IDE and the dialysis staff working in the unit. The overarching aim was to describe perceptions of IDE, and its key components and unintended consequences. Key components are those aspects of the intervention beyond the exercise itself that are critical to enhancing effectiveness.[20] To determine whether aspects of the IDE intervention required adjustment prior to scaling up,[21] we also aimed to understand the unintended consequences (positive or negative) of implementing IDE.

4.3 Methods

4.3.1 Design and setting

This qualitative interpretive descriptive study was carried out in three phases coinciding with a single-center, pilot RCT (registration number NCT02234232). The primary aim of the RCT was to evaluate the feasibility of two types of IDE, cycling and weights, compared to control. The setting was an outpatient dialysis unit servicing approximately 110 patients and employing 35 staff, in a tertiary hospital in Edmonton, Canada. The interviews were conducted in three phases (Figure 4-1). A kinesiologist supervised most exercise sessions. Staff were in-serviced on how to assist with exercise equipment set-up and on trial documentation. After the trial, participants could continue IDE with assistance from the kinesiologist and staff.

Our methodological approach was interpretive description (ID).[22,23] ID was developed for answering questions in health care, where the aim is to generate recommendations for clinical practice. This approach provides a systematic and inductive framework for identifying common patterns from a range of individual experiences and aims to explain these patterns in the relevant social context.

4.3.2 Participants

Participants were purposively selected from those impacted by IDE: renal program administration, patients in the study unit, trial participants, and dialysis staff. This manuscript presents findings from interviews with staff and trial participants (phases two and three). Staff (RNs, LPNs, technicians, service workers) were eligible to participate if they had worked in the unit during the trial. This study was conducted in a satellite dialysis unit where nephrologists are not generally present, therefore nephrologists were not interviewed. After trial participation was complete, patients were approached for interviews by an investigator (ST); participation was voluntary. The Health Research Ethics Board at the University of Alberta approved this study and all participants gave informed consent.

4.3.3 Data collection

Staff participants were interviewed by telephone by an experienced qualitative researcher not involved with the trial. Staff interviews lasted 10-20 minutes. Patient interviews took place either face-to-face at the hospital site or by telephone, according to individual preference. Patient interviews ranged from 15 to 45 minutes and were conducted by ST, who had established a relationship with the participants during the trial. The interviews followed a semi-structured format (Table 4-1). All interviews were audio recorded and transcribed verbatim. The transcripts were verified against the audio recordings. Field notes were made after each interview.

4.3.4 Data analysis

Data collection and analysis were conducted concurrently so that new concepts could be explored in the remaining interviews. ST is a nephrologist who was not involved in the clinical care of the patient participants but she had an understanding of the contextual factors.

ST independently coded the interviews using a broad-based coding scheme (open coding). Codes were revised and reviewed for each individual interview and grouped into common themes. Themes were then compared across interviews. Codes were annotated to show the inductive reasoning process. To confirm that the beginning conceptualizations were consistent with participants' experiences, preliminary themes were distributed to the participants (separately for staff and patient participants). Several staff and approximately half of the patients responded. All respondents agreed that our thematic conceptualizations were consistent with their experiences. Theoretical saturation was reached.

4.4 Results

We interviewed 11 staff in phase 2, and 25 of the 31 trial participants in phase 3 (Figure 4-1). Staff were primarily Caucasian women and registered nurses (Table 4-2). The median age of staff was 42 years (interquartile range, [IQR] 30.0, 52.0). The median age of patients was 57.5 (IQR 49.2, 68.0). Patient participants were predominantly Caucasian males; 88% had hypertension, 52% had diabetes. The median age of the six non-participants was older (69.8 years, IQR 49.5, 85.0); four patients were Caucasian, one was Asian, and one was Indian.

Interview themes and subthemes

Three main themes were common to staff and patient interviews: support; the role of the dialysis nurse; and norms within the unit. "No time" (to support IDE) and patients getting their own exercise equipment were unique themes in the staff interviews. Social interaction was an additional theme from the patient interviews. Themes with associated subthemes and exemplar quotes are shown in Tables 4-3 to 4-8.

Support

After hearing of the benefits of IDE from their patients, staff agreed that the exercise program was valuable for patients (quote 1 [Q1]). However, systemic factors may have influenced staff perspectives of IDE. Changes to staffing ratios on the unit were to take effect in several months, unrelated to IDE, but coinciding with initiation of the clinical exercise program. The knowledge that staffing was going to be "*cut back*" conveyed a lack of support from management (Q2). Several staff expressed uncertainty about need for these changes and expressed concern over how workflow in the unit might be affected (Q3). One staff suggested that these changes could be detrimental to patient care overall and expressed doubt in their capacity to consistently participate in IDE delivery (Q4).

Participants identified the staff and the kinesiologist as the main sources of support during the study. Several patients expressed that the staff encouraged their participation in IDE typically through simple words of encouragement (Q5, 6). One participant could not define how support had been conveyed to her but the staff's reaction to IDE had given her a sense of esteem (Q7).

It was more common for patients to comment on the inconsistency of the staff's involvement. Many participants described lack of support in the form of inconsistent help with the exercise equipment (Q8); several participants attributed this variability to the nurse (rather than situational factors) (Q9). For some patients, the staff were perceived as inaccessible for help (Q10). Another participant expressed frustration with the staff's lack of accountability explaining that asking for equipment from particular staff members was such a "*struggle*" that he did not participate in IDE when those staff were working (Q11).

Patients commonly viewed the kinesiologist as the primary source of support for IDE. Some participants perceived support from the kinesiologist in the form of technical instruction and trusted her expertise and knowledge (Q12). For most patients, the kinesiologist's technical instruction was interpreted as having emotional meaning. Patients expressed that they gained confidence in their physical capabilities from training with the kinesiologist. The caring and esteem conveyed in the actions of the exercise specialist enhanced patients' body confidence, sense of capability, and feeling like an individual (Q13-15).

The role of the dialysis nurse

Although staff recognized the benefits of IDE, they commonly expressed that assisting with IDE was not a nursing responsibility. One staff member indicated that it was the exercise (rather than assisting with a study) that was inconsistent with their role (Q16). Another staff member explained that tasks, such as IDE, were left to them by default (Q17). Although staff did not express safety concerns with IDE; one person expressed concern whether patients were '*doing it [the exercises] right'* and commented that staff could not monitor this (Q18).

Staff frequently described their involvement in IDE in technical and procedural terms (getting equipment, documentation) and their role in encouraging patients was not commonly described. In the interview where encouragement was discussed, the staff member commented that patients would find encouragement to exercise more effective if it came from physicians, suggesting that staff may not appreciate their role in patients' decision to exercise (Q19). Understanding of IDE could also influence staff interaction with patients. Several staff were surprised that the elderly patients had the physical capacity for IDE—while other patients, perceived as more suitable, were not interested (Q20). One staff member expressed that many patients in the unit were too immobile and sick to participate in IDE (Q21).

As patients commonly viewed IDE as beneficial, many expressed that staff involvement in IDE was consistent with their role as carer and advocate (Q22). Patients described the staff's role as providing encouragement and assistance with the equipment (Q22, 23). Most patients were aware that the staff saw IDE as *"extra work;"* however, many patients believed that staff participation in IDE was feasible (Q23, 24). One patient expressed resignation about the situation as he viewed systemic factors as a limitation to their involvement (Q25); other patients viewed staff involvement as nurse dependent (Q26). Several patients viewed the more physically active staff as more interested in participating in IDE (Q27).

Norms within the dialysis unit

Many of the staff expected that prior to asking for help with IDE, dialysis-related tasks at the start of the shift were completed (Q28). Initiating IDE at the start of the shift was challenging and some staff expressed frustration about how to effectively communicate with patients about the timing of exercise during dialysis (Q29, 30). One staff member indicated that negotiating aspects of HD delivery with patients was a pre-existing issue suggesting that IDE may have been an additional pressure (Q31).

Patients described aspects of the unit's social structure that were barriers to receiving assistance with IDE. Some participants were concerned that IDE would disrupt the "*routine*" of the unit (Q32). The existing processes for obtaining help from staff (ringing the bell) were viewed as inappropriate for IDE (Q33). One patient expressed concern that using the bell for help with exercise could have negative consequences when help was urgently needed. For one patient, not being a "*bother*" by asking for things was important to the role of the "good patient" (Q34).

"No Time"

Many staff commented that there was "no time" to assist patients with IDE. The expectation that staff had the time to participate may have negatively influenced some staff's attitudes toward

IDE (Q35). For some staff, "no time" also meant that IDE was a low priority in their workflow and IDE was seen as *"extra work"*. One staff member questioned the appropriateness of exercise for the dialysis unit (Q36). Another attributed their lack of time to the unpredictability of staffing and patient acuity. Staff often expressed that due to the demands of the unit, the situation was irremediable (Q37).

Patients getting their own equipment

There was agreement among dialysis staff that IDE would be more sustainable if patients set up their own exercise equipment (located in the unit) prior to treatment. Although several staff expressed they could help frailer patients with their equipment, other staff commented that this was not feasible (Q38). Getting one's own equipment was valued for "*saving [staff] time.*" More commonly, this task was valued as a sign of the patient taking responsibility for their care (Q39).

Social interaction

Many participants described enhanced social interactions with other IDE participants. Several of the male patients discussed instances where they were competing with other trial participants. These interactions were perceived as positive and promoted a sense of camaraderie and normalcy within the unit (Q40, 41). One participant said that IDE was a positive topic for patients outside of the unit and that she thought it had improved spirits. (Q42). Another participant explained that IDE fostered a more positive common identity (Q43).

4.5 Discussion

Despite the promising results of RCTs, IDE remains underutilized. By identifying the key components and unintended consequences of IDE, we address an important gap on the transferability of research findings to practice. Our study provides insight into what aspects of

IDE enhance its effectiveness when adapted to different contexts.[24] Detecting positive unintended consequences of IDE could increase perceptions of its value. It is also important to identify the negative consequences of IDE before scaling it up.

Although the importance of staff professional support in sustaining an IDE program has been recognized,[25,26] how support functions to enhance the effectiveness of IDE and what may be required from those delivering IDE is unknown. We identified the support of the kinesiologist as a key component of IDE implementation. Social support is a multi-dimensional concept that includes emotional (communication of empathy and esteem) and instrumental support (offering assistance and information).[27] Previous publications have emphasized the technical role of the exercise specialist in IDE,[25,26] consistent with instrumental support. However, it was the emotional interpretation of this technical support that appeared critical to enhancing perceptions of the intervention's effectiveness and facilitated high acceptability of IDE. In one study in people with ESRD, higher levels of perceived social support, regardless of domain, predicted improved outcomes, such as QoL.[28] Consistent with other research,[27] we found that the emotional aspect was the most effective component of social support.

Maintaining norms within the dialysis unit was another key component of IDE delivery. Initiating exercise at the busiest time of the shift was a barrier to staff participation. Although patients viewed IDE as consistent with the staff's role as carer, reluctance of some individuals to ask for help suggests that exercise was not an expected aspect of the dialysis treatment. In another study,[29] patients perceived IDE as potential burden to staff but staff perceptions were not explored.

We found that IDE promoted social interaction among trial participants and promoted camaraderie and normalcy. Given that HD patients rate the quality of their social interactions as low,[30] greater social interaction could be a benefit of IDE. As social interaction with other dialysis patients is a positive aspect of in-center HD,[31] IDE could improve outcomes such as satisfaction with care. For staff, IDE was an opportunity for patients to increase responsibility in their care by getting their own exercise equipment. The extent to which this view was grounded in values of self-care, or was simply about 'pitching in' warrants further exploration. Framing IDE within unit priorities, such as promoting self-care, may facilitate IDE uptake whereas an emphasis on pitching in may exclude frailer patients needing more help.

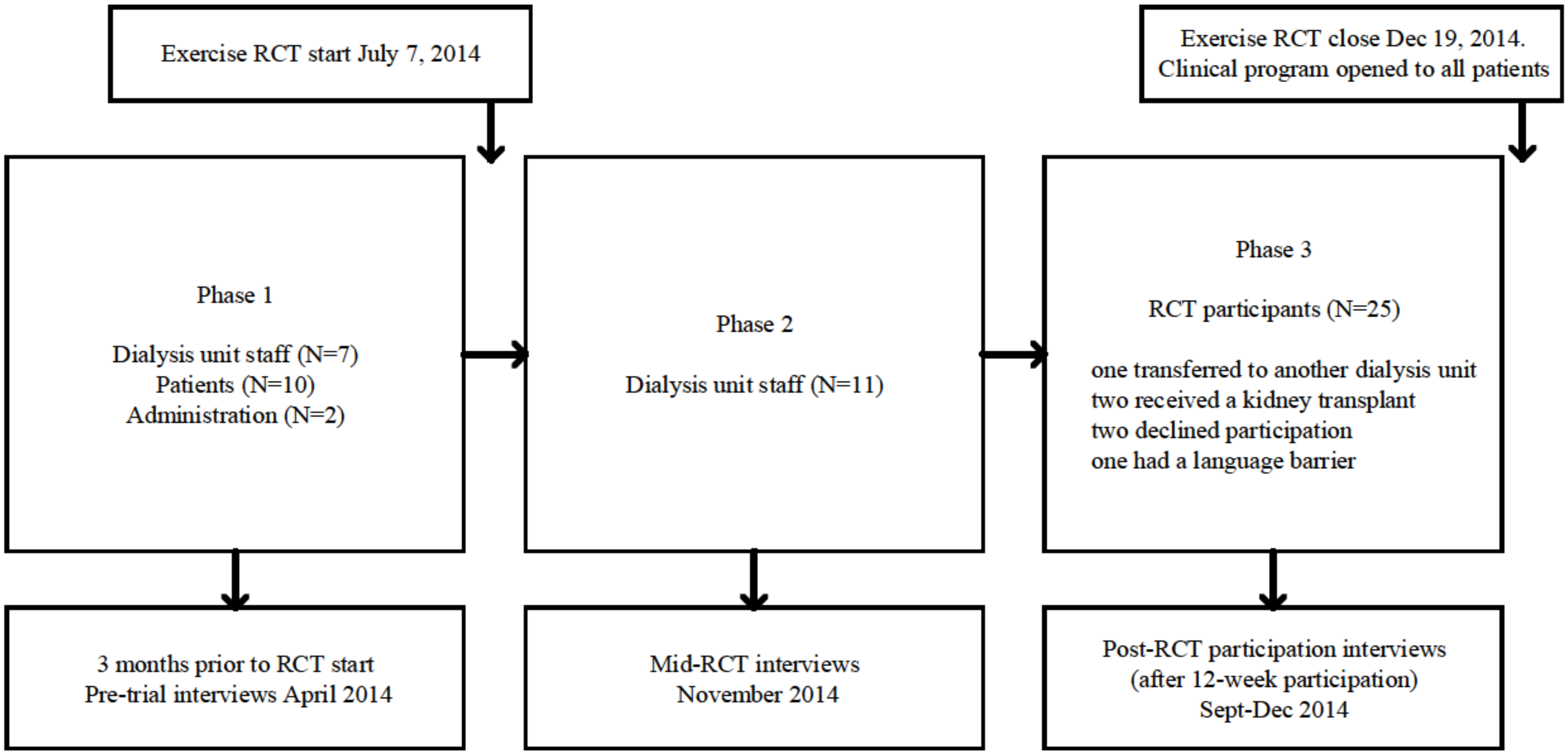
Emphasis on the technical aspects of the dialysis nursing role is not unique to participation in IDE and has been explored in other studies.[32] In one study,[33] the increased workload in the unit and the resistance to take on new roles were factors contributing to technology-focused care. In our study, staff participants discussed several systemic factors that influenced their perceptions of their role in IDE. First, there was a perceived lack of support from management—expressed as lack of adequate staffing. Second, consistent with findings from other studies on IDE,[15,34] staff frequently mentioned there was "no time" to assist with IDE. Given the high value placed on 'busyness' in acute care nursing,[35] the assumption that staff could accommodate IDE in their workflow may have negatively influenced its acceptability. The view that dealing with acute issues superseded staff capacity to take a consistent role in IDE also reflects the values of an acute care culture, where the urgent takes precedence over other important roles. Reconciling this acute care mentality with the competing priorities of chronic disease management is particularly germane for in-center HD units.

Consistent with previous research, despite the staff's perspective that exercise was beneficial for patients,[34,36] there was a lack of readiness for IDE.[34,37] Our results extend these findings by identifying important considerations in implementation of IDE. First, it is important to recognize that structure of work and perceived value of tasks is grounded in organizational culture.[38] For staff to prioritize IDE, management's support of IDE must be evident to staff. In this context, support could be conveyed to staff by ensuring that adequate time is created in the staff's workflow to accommodate participation in IDE. Second, at the individual level, increasing staff knowledge of who can perform and benefit from IDE may improve acceptability. Prior to implementing formalized education on IDE, it is necessary to increase staff motivation to engage with IDE. Some patients perceived that more physically active staff were more involved in IDE, suggesting the role of the nurse in IDE is influenced by personal values about exercise. As exercise is a socially desirable behavior, initiatives that concurrently encourage staff exercise may promote engagement in IDE.

Although the qualitative approach does not aim to generalize results, our findings should be considered in light of our study's limitations. The specific context of the unit, including readiness for IDE, physician and administrator involvement, and organizational culture may influence findings and therefore the transferability of findings to other centers, particularly those with different models of care, may be limited. Second, although it is possible that participants provided socially desirable responses in interviews, the candid responses from participants suggest they were able to speak openly. Third, due to the lack of diversity in the demographics our study population, we did not analyze our findings according to these characteristics.

We identified important areas for future study. It would be useful to explore what characteristics of exercise specialists and the specialist-patient interaction are associated with improved effectiveness of IDE. Our results expand our understanding of the decisional influences on patient participation in IDE beyond individual factors to include those that exist at the contextual level. Future studies should consider how contextual factors may affect adherence to IDE, rather than attributing poor adherence to lack of patient motivation.

Figure 4-1. **Flow of interview participants in relation to the RCT timeline**. Over phases 1-3, approximately 35 unit staff were working in the unit. In phase 3, 25 of the 31 RCT participants participated in interviews



RCT=randomized controlled trial

Table 4-1. Semi-structured interview questions for dialysis staff and trial participants

Unit Staff	Trial participants
Can you give a description of your involvement in the study?	What was it like for you to participate in the study?
What was it like for you to participate in the study?	How would you describe the experience to another person who was considering participation?
Were there any challenges/benefits to having the exercise program in the dialysis unit?	Were there any benefits/challenges to doing exercise here in the dialysis unit?
Is there anything that you think researchers or health care professionals interested in starting dialysis-based exercise programs should know?	Did anything change for you as a result of participating in the exercise program?
	What would you change about the program if you could?
	Is there anything that you think researchers or health care professionals interested in starting dialysis-based exercise programs should know?

Table 4-2. Characteristics of staff and patient participants

Dialysis staff (n=11)		**Patients (n=25)**	
Age, y[1]	42 (30.0, 52.0)	**Age, y**[1]	57.5 (49.2, 68.0)
Female	10 (91)	**Male**	19 (76)
Ethnicity	Caucasian=7 (64) Asian=3 (27) Southeast Asian=1 (1)	**Ethnicity**	Caucasian= 16 (64) Aboriginal=3 (12) Indian= 3 (12) African= 2 (8) Hispanic=1 (4)
Years of experience[1]	8 (6, 16)	**Years on hemodialysis**[1]	3.5 (1.8, 4.2)
Position	RN=8 (73) LPN=2 (18) Tech=1 (9)	**Hypertension** **Diabetes** **Stroke** **Coronary artery disease**	22 (88) 13 (52) 6 (24) 2 (7)

1. Median (IQR interval), otherwise N (%)

Table 4-3. Exemplar quotes from staff and patients on the theme of support

Support	Quote
<u>Dialysis staff</u>	
Support and recognition of the benefits of IDE	*"No, I think it's a really great program and I've had a lot of really positive feedback from the patients saying they have better energy levels, that they're feeling healthier. So I'm very much about implementing the program on a more regular basis for dialysis patients" Q1*
A lack of support from management	*"Right now is okay, but the only thing is I think also there is going to be some transitional—we're going to have some changes on the staffing ratio on our unit, and they're going to cut back on us, so it's going to be some time during the day that they're going to cut back; like, now we have nine staff, and they're going to cut it back down to six staff…"* Q2
Doubt in their capacity to assist with IDE	"*…So I don't know how well, how much it will be affecting the [exercise] program, is going to be permanent for our patients. Because they don't want that many—well, management has a reason to cut the staff, but we still have to wait and see what's going to happen…"* Q3
	"Well, things are changing for our unit and how the unit is run, so we're going to be doing, like, different times and team nursing and everything, so we're not going to have a lot of extra time to be helping patients with this [IDE], and it's going to—we're going to be short-staffed—they're going to take some staff ratios away. So it's really going to affect us as well as the patients…" Q4
<u>Patients</u> *Encouragement from dialysis staff*	*No, not really, other than the fact that—well, the nurses actually encouraged then [when the study staff were not there]; they were the ones that said, "Go faster __________ !" ..So just the encouragement, probably….it was really good; it was helpful."* Q5
	"…they were cheering us along—well, really, I can speak for me—they would be cheering me along and giving me compliments and just encouraging me, telling me how well I'm doing, and telling me they see a change in me. "Q6
	"I think—I felt that the nurses were impressed; that's one feeling

	*that I got. I don't know for sure, but that's one feeling that I got, that they were impressed that we were doing this."*Q7
Inconsistent help from dialysis staff	*"I know the nurses don't like doing it. They don't ask you and they don't remind you, "Are you going to do your exercises?" Some do, some don't."* Q8 *"It depends on the nurse you have. Some days it will be problematic [getting help with the equipment], other days, it'll be just fine. Depends on who your nurse is that day."* Q9 *"Well, unless you're willing to ring the emergency bell and get them to come over just to ask for your exercise equipment, you're practically waiting for one of them to walk around."* Q10 *"Oh, I was totally motivated, but again, it was the struggle of, "Oh, well, you know, I guess maybe I won't be doing it because I just don't feel like asking this particular nurse. Then I don't want to ask, let's say, [person D], who's not my nurse, "Can you get it for me?" You know what I mean? 'Cause the first reaction is, "Well, who's your nurse? How come you didn't ask her?"* (Q11).
Increased body confidence and sense of capability through technical instruction	*"She, you know, puts everything on and makes sure that I'm doing it properly. And that's good, too, because you can hurt yourself if you don't do it properly."* Q12 *"I'm going to continue on my own, because you [the exercise program] already gave me the tools to work with and I already could see what it does to my life and to my personal life, my personal self, my health life—I see what it does for me."* Q13 *"She was so encouraging that it makes you want to do it. I found I could do more than I thought I could."* Q14 *"She helped me with what level I should go to and what I could handle, and that way, I felt very good about that."* Q15

Q=quote

Table 4-4. Exemplar quotes from staff and patients on the theme of the role of the dialysis nurse

The role of the nurse	**Quote**
Dialysis staff *IDE is not the nurse's role*	*"Well, it's some extra work, to be honest. Yeah. At first, it was kind of—well, we have a couple of studies ongoing, besides the ones that we have to do as a nurse for our patients and then answering alarms. "* Q16 *"Yeah, pretty much it's the staff who will be doing it hands-on, like, because I don't know if they're [the study staff] going to be here for, let's say, the whole time for that study or not, it just falls to the nurses who's also doing the things that they have to do. Know what I mean?"* Q17 *"So that's the hard part, I find, like, with patients who don't know as well as others know, what they have to do. I think we have to do some minor adjustments on the bikes; seems to be a little bit more tension, just a little bit less tension, that's something it's quickly, we can do that and walk away; they'll carry on with whatever they are doing. But some patients, like I said, who are not—I can't say with it, but not as comfortable maybe doing the exercises as others, it's a little harder to—for us to monitor whatever they do is proper. I don't know, it's maybe they need a bit more education or its maybe they are not good people for the study."* Q18 *"No. I think it's just who it comes from is definitely the importance. They tend to put a lot of trust in the doctors, so I believe if it [encouragement] comes from a doctor, then it would affect their thinking a little bit more than if it was to come from a nurse or somebody that does exercise and is promoting the exercise. I think if it came from a doctor, the importance of it, then it probably would be more important to them."*Q19
Awareness of their role in IDE	*"Yeah. It's actually pretty surprising. Some patients that you wouldn't think would have the stamina really enjoyed it and really did the bike for, like, 45 minutes."... and some patients you would think that would appreciate doing it didn't want to become involved."....some of the patients, like, in their 70s, 80s, really enjoyed it."* Q20

Knowledge about IDE	*"I think they're [study staff] limited to the number of patients that they have on there, just because of our patients—the patients that we have there…their mobility is decreased already, they're sick."* Q21
<u>Patients</u> *IDE is the nurse's role*	*"But I was also kind of disappointed that they weren't more enthusiastic about having the patients maybe do a task, enjoy their task, occupy their time more, and to have a benefit to the patient… That's what—that kind of wasn't—didn't sit well with me necessarily, that that they should be willing to do everything for the patient…"* Q22 *"I mean, even if I'm done my leg exercises and I'm sitting there with 5 pounds of weight on each ankle, I still need someone to undo that, get the bike, get it set up and ready to go for the next thing. And you're busy or [person A]'s busy—whoever's there—so the nurses could handle that job quite easily." Q23* *"It's one more job for them. I've heard from other nurses that, "Oh, this is—why do we have to do this? Q24* *"I think that they should realize that exercise is important for us people, and that they should maybe show a little more enthusiasm towards us doing some exercise. But I know that they're overworked and understaffed, so what can you say?" Q25*
<u>The influence of personal values about exercise</u>	*"It depends on the nurse you have. Some days, it'll be problematic, other days, it'll be just fine. Depends on who is your nurse that day." Q26* *"…she [the nurse] would stop and chat about the stuff and she'd get a rubber band and do some exercises, too… You know, because she exercises a lot herself, right?" Q27*

Q=quote

Table 4-5. Exemplar quotes from staff and patients on the theme of norms in the dialysis unit

Norms within the dialysis unit	**Quote**
Dialysis staff Knowing to wait	*"Oh, it [IDE] hasn't been bad at all. As long as the patients are understanding that I can't do it, like, right now, 'cause I still have somebody else to put on, and most of them were pretty good about that."Q28* *"..But for us, sometimes we still have other patients to take care of, put patients on, and so sometimes we don't get there until an hour or even 2 hours later."Q29* *"They're quite—they have quite negative comments if we can't get to them in the time that they want. So unfortunately then the discussion of "Well, there is only two hands," blah blah blah blah. So that's a bit of the unfortunate thing."Q30*
IDE as an additional source of pressure	*"Well, we have 18 patients and sometimes our patients are late or we're short-staffed, and we have patients that are quite demanding; they're, like, "We have to do it now." And we know they don't, but sometimes it's just hard, you just don't want to argue with your patients."Q31*
Patients *Keeping the routine*	*"…if we want something to do with the equipment, we would have to push the red button, which somebody up front's got to answer the red button, and it disturbs—then it would disturb everybody's routine."Q32* *"They're never just convenient to wave down. You know, you've got to ring your bell, and then if you start ringing your bell for frivolous things, then they start ignoring you later when you really need them to come when you ring the bell."Q33*
Don't be a bother	*"I don't like asking them for anything. I'm just not that kind of person. I've never asked for help in my whole life. I'm just a person that goes and do stuff. But I suppose I could. I mean, like, when I want my cup of tea, I usually wait until one of them will come, and then I'll ask—although this morning, I didn't; I had to call them. But I don't like to bother them, because they're busy, and so I try and bother them as little as possible, and I think they appreciate that."Q34*

Table 4-6. Exemplar quotes from staff on the theme of "no time" to assist with IDE

"No time" to assist with IDE	Quotes
IDE as a low priority	*"I do know before the actual program started, I believe there was talk of the nurses taking on the role, and I don't know if that was true… a lot of the nurses were not impressed, and they discussed that, that there's just not time for that."Q35* *"[Do the exercise] Before they start dialysis, because it really is, like, here sometimes we have people come late or whatever, we're busy, because something is seriously wrong with one of the patients, you just don't have time; actually, you just don't have time to do it. There's already stuff that we're supposed to do that we don't have time to do." Q36*
High demands on the unit	*"No, because even though if we are so-called satellite unit, people sometimes they feel sick and then they couldn't do it and then we are busy, then we couldn't help out with having the exercise done, and then we just have to leave it for [the kinesiologist] to come. If they don't come that day, they just have to skip the exercise. Yeah, 'cause, still, that is not the priority, is to help our patient's safety, right? If they don't feel good and some other emergency—that we have to deal with an emergency instead of helping them out with the exercise."Q37*

Q=quote

Table 4-7. Exemplar quotes from staff on the theme of patients getting their own equipment

Patients getting their own equipment	Quotes
What is practical for staff to do	*"Well, my thing is not that I would not want patients to not do the exercise program, but again, if they were going to be taking away the kinesiologist and they would want to just implement the program in general, I would really cater it more to the independent patient that could grab their supplies for themselves and record their own blood pressures and things like that for further study, versus that being the nurse's job, because sometimes if there's an acute situation, again, the patients are stuck in the chair and there's nothing they can do, but whereas if they come in and got their own supplies, there are still things that they can do, regardless of whether the nurse is there." Q38*
Patients should take responsibility	*"Good patient education. I think that that would be number one [for the sustainability of the program], is really strong patient education, that they are doing this for their benefit, that this is what benefits them, and that they are responsible to at least make an effort in getting their own supplies, like the weights or the bikes, and if they need help, to ask us. But I think number one is it's just so key that it's patient education, that they understand it's their responsibility." Q39*

Q=quote

Table 4-8. Exemplar quotes from patients on the theme of social interaction

Social interaction	Quotes
Camaraderie and normalcy in the unit	*"Yeah, it's positive. And especially guys, guys enjoy that. If you've been around guys, sports guys and things like that, that's the thing to do. And it makes the dialysis environment a lot more pleasant…There's more excuse now to yell across the room."Q40*
	"I'll raise the bar. Maybe somebody else will want to—when I was cycling the other day there, my neighbour, he said, "Maybe I should have a race with you." I says, "Well, bring it on, bring it on." Q41
Fostering a positive common identity	*"Like, we're really, really close, we're kind of like a little family, and we're all down—like, we all meet downstairs...they would say things as, "Oh"—they liked it [IDE], they really looked forward to it, they looked forward to it when they come here. One of them down there, he—I asked him if he was going to continue once the program was done, and—but I just found him to be a little—I thought he was maybe a little older, a little tired, but no, he was—he says he notices how even his spirits—and even when we go downstairs, like, he's just all chirpy and happy about it"Q42*
	"Like, you can ask us dialysis patients when we're sitting waiting around for each other or when we're dialyzing beside one another, it's just something—another exciting thing that, yes, we have dialysis in common, but now this is a positive thing we have in common that we can talk to each other about and encourage each other with."Q43

Q=quote

CHAPTER 5

INCREASING THE UPTAKE OF EXERCISE PROGRAMS IN THE DIALYSIS UNIT; A PROTOCOL FOR A REALIST SYNTHESIS

5.1 Abstract

Introduction

For people with end-stage kidney disease on hemodialysis, exercise during the dialysis treatment (intradialytic exercise) may promote exercise adherence and enhance aspects of the dialysis treatment. However, intradialytic exercise programs are complex and how to adapt program components to local context so that the program is more likely to attain its intended health outcomes have not been well described. To increase the uptake of exercise in clinical practice, more evidence is needed on how contextual factors influence the program's impact.

Methods

Using the realist approach, we aim to understand how the processes and structures of intradialytic exercise programs work to influence patient participation according to different contextual factors. The focus of a realist review is explanatory and aims to develop and test theory on how contextual factors trigger specific processes or behaviors (or "mechanisms") to produce outcomes. Using the realist context-mechanism-outcome configuration of theory development, we will use a range of sources to develop initial candidate theories: a scoping review of published papers and the grey literature, and discussion with stakeholders. To provide a theoretical basis for how contextual factors could work to influence patient participation in IDE, several of our preliminary theories will be based on dominant theories of exercise adherence and behavior change. To support or refute these initial theories, we will synthesize

data from a systematic literature review and semi-structured interviews with intradialytic exercise program stakeholders, sampled from a range of programs worldwide.

Discussion

The complexity of intradialytic exercise programs poses challenges to their implementation. Using the "context, mechanism, outcome" approach, the knowledge gained from this study will be used to develop general recommendations for renal care providers and administration on how to adapt components of an intradialytic exercise programs according to different contextual factors in order to promote patient participation.

PROSPERO registration number: CRD42016033335

5.2 Introduction

Chronic kidney disease (CKD) is associated with high cardiovascular mortality[1] and markedly reduced quality of life.[2] Systematic reviews of interventions using regular exercise training suggest that exercise is a promising means of improving these outcomes in people with CKD: regular exercise is associated with improvements in cardiovascular fitness,[3–5] heart-rate variability,[4] and the physical dimension of quality of life (QoL).[3]

Despite these benefits, people with CKD report a low level of physical activity.[6] For those people with advanced kidney disease requiring dialysis, self-reported physical activity is below the fifth percentile of the general population.[7] One of the barriers to exercise participation in this population is the hemodialysis treatment itself, which necessitates 12-18 hours per week spent in a health facility.[8] One means of effectively addressing this barrier is to recommend exercise during the dialysis treatment (intradialytic exercise, [IDE]). Aside from convenience, there may be important advantages to performing exercise during the dialysis treatment, such as decreased severity of restless legs,[9] improved dialysis adequacy[10] and increased enjoyment of dialysis time.[11] In clinical practice however, IDE programs remain the exception rather than the rule. Several proposed explanations for the low uptake of IDE programs in clinical practice are: the unknown effects of exercise on "hard" outcomes, such as survival;[12] the uncertainty on what exercise to recommend to patients for optimal benefit; and the methodological limitations of existing exercise RCTs specifically, the lack of blinded outcome assessment.[3] Yet even if these questions on efficacy are addressed, there is still a largely unaddressed evidence-practice gap about how to adapt the components of IDE programs to different contexts so that the program achieves its goals. This question is relevant for IDE program development because these programs have varying components, are heterogeneously delivered, and are implemented in complex and diverse settings – so what works in one setting may not work in another. A better understanding of the processes and structures that are necessary for the program to attain its effects can inform site-specific adaptation and also potentially enhance program effectiveness.[13]

Although there is no absolute definition of what makes an intervention complex, the following description offers some guidance: complexity is introduced in an intervention by the number of interacting components; the number and difficulty of behaviors required by those delivering or receiving the intervention; the number of groups or organizational levels targeted by the intervention; the number and variability of outcomes; and the degree of adaptation or tailoring of the intervention to local context that occurs.[14] IDE programs satisfy this description of complexity. First, in addition to the exercises, exercise programs also include educational and psychological components. Second, IDE programs require dialysis unit staff to accommodate exercise (or exercise recommendations) into their workflow and for patients to exercise during a time that was previously restricted to sedentary activities. Third, to accommodate exercise in the dialysis unit, renal program managers may need to implement new unit policies and procedures. Fourth, the resources available for IDE programs will vary across different settings and will naturally result in local program adaptation. For example, there may be differences in the types of equipment that are available and in the skills and the experience of the staff who deliver the program (exercise therapists versus unit staff versus self-directed).

Understanding the complexity and context-sensitive nature of IDE programs has important implications for how these programs are evaluated. Although an RCT is the optimal study design to answer the question of whether the intervention works, it is not designed to answer the question of how a program achieves its effects. In addition, a potential barrier to the uptake of positive findings from RCTs is the insufficient information on the intervention and context.[15] To our knowledge, there have been no reviews in which the complex and multifaceted aspects of an IDE program or how these might work to influence program effectiveness have been systematically evaluated. This realist review aims to define the causal links between IDE programs and their intended outcomes (the program theory) and provide an understanding of what components of an IDE program are important for its success (or failure).

5.3 Methods

The overall aim of this realist review is to understand how contextual factors trigger the mechanisms that influence patient participation in IDE programs. Mechanisms are the processes or structures that work according to specific contextual factors to generate an outcome of interest.[16] As different clinical IDE programs will use different outcomes to measure program effectiveness, the outcome of interest in this review is patient participation (recognizing that patient participation in IDE is necessary in order to obtain health benefits).

Our specific objectives are

- To identify the program theories on how IDE works to promote patient participation in exercise.
- To identify the contextual factor(s) that triggered the mechanism(s) to influence patient participation in the IDE program.
- To identify and explain the mechanisms that influence patient participation in IDE programs

- To use empiric data synthesized from a systematic review of the literature on IDE programs and interviews with IDE program stakeholders to test and refine our initial program theories

In addition, as patient participation in an IDE program represents only one stage of the implementation process, theories will also include contextual information on program development and delivery.

In general, programs are implemented with assumptions as to how they work to bring about their intended outcome(s). Realist review uses a systematic and theory-driven approach to refine these assumptions into theories that can then be empirically tested.[17] In a realist synthesis, the theory of how a program "works" is structured according to the 'context-mechanism-outcome' (C-M-O) approach.[18] That is, the program theory is explained as the contextual (C) factor hypothesized to have triggered the relevant mechanisms (the underlying process or behavior) (M), to generate the outcome of interest, (O).[19] The process of a realist review is focused on identifying, explaining, and testing these semi-predictable, context-mechanism-outcome (C-M-O) patterns (called "demi-regularities").[17] C-M-O configurations form the basis of the program theory known as "middle range"[20] theory. A middle range theory is abstract enough to be generalizable but is also close enough to the data that it can be empirically tested. For example, a theory might emerge that HD units that have a dedicated exercise expert delivering IDE (the context) increase participants' confidence in their physical capabilities and body knowledge (the mechanism) thereby facilitating regular participation in exercise (the outcome).

5.3.1 Study design

This realist review was based on the approach of Pawson et al.[17] and is consistent with publication standards for realist reviews (RAMESES criteria).[19] An overview of the stages of the review is shown in Figure 5-1.

5.3.2 Identify candidate theories

We will start with provisional program theories on how IDE works to facilitate patient participation in exercise. Development of these initial "candidate theories"[17] is a speculative process and will be refined in future stages of the review. We will use a number of methods and sources to derive these candidate theories: a rapid review of studies and reports on clinical IDE programs, examination of theories of behavior change related to exercise programs, and consultation with individual experts in the field. We will focus on identifying potentially influential contextual factors as defined by Pawson et al.,[17] specifically, the individuals (skills, knowledge, and roles of those delivering the program); the lines of communication (among staff and different organizational levels); the institution (job descriptions or policies that incorporate aspects of the program); and the program's resources (funding, space, equipment, and incentives).

5.3.3 Data collection

To test our candidate theories, both primary and secondary data will be used. The literature review will include a broad range of sources and primary data will be collected through individual interviews with IDE stakeholders. The ethics review board at the University of Alberta has approved the study (Pro00057423).

Literature search

The search strategy will include a systematic search of the literature. In searching the literature, we aim to identify papers that focus on patient participation in clinical IDE programs. We will use the skills of a specialist librarian to develop initial search terms, revise the search as required, and to identify relevant data sources. There will be no restrictions on publication type. The search will be restricted to the English language and will include a focused search of the unpublished and grey literature (i.e. thesis dissertations and renal rehabilitation websites). We will use hand-searching and pursue references of references. Studies that discuss participation in IDE programs only in terms of trial enrollment will not be included. ST will screen articles for inclusion based on title, abstract, and keywords against inclusion criteria. Potentially eligible studies will be obtained in full text and rescreened. Another investigator will review a random subset of the full articles. The decision to eliminate an article will be discussed with the study team and reasons for exclusion will be documented.

Semi-structured interviews

Our initial search of the literature indicates that few existing publications on IDE include sufficient information to inform the development of our initial program theories. Therefore, we will obtain additional information through individual, semi-structured interviews with IDE stakeholders. Using the results from our literature search, maximum variation sampling according to geographic location will be used to capture the variation in IDE programs. Where possible, we will also select sites based on known variation in contextual factors, such as program delivery and resources. We aim to interview champions of clinical IDE programs—those who play a key role in sustaining the programs. To identify these champions, we will contact the corresponding authors of the included studies or reports from our literature review. In cases where there is an individual perceived as more knowledgeable on the clinical aspects of the program, we will approach this individual for an interview. Eight to ten interviews are planned (or until theoretical saturation is reached). Potential participants will be informed about the study through an emailed letter of information and online access to the protocol. The decision to participate in the study implies consent. The interview questions will be piloted at two IDE programs and revised accordingly. All interviews will be transcribed verbatim for further analysis. The interview questions are aimed at understanding service provider perspectives on the link between processes, behaviors, and outcomes according to various contextual factors. To include IDE programs that are not represented in the literature, we will use snowball sampling. Interviewees will be asked for the names and contact information of sustainers in other IDE programs. The study will be advertised on select renal websites.

5.3.4 Data extraction and study appraisal

The following manuscript characteristics will be extracted and tabulated on an excel spreadsheet: objectives, study design or publication type, size, setting, contextual components, and mechanisms (how the intervention may have "worked" to trigger change) and manuscript quality. One author will extract data and another will check for accuracy. We are focusing on patient participation as an indicator of program effectiveness; however, we recognize programs may use different measures of effectiveness and we will discuss these outcomes in the analysis. Study quality will be judged according to quality standards appropriate for the type of research (rigour) and on relevance (whether the manuscript contributed to theory building).[17] Two reviewers will evaluate the relevance and rigour of the included studies. Any disagreement will be resolved through consensus-based group discussions with the study team.

5.3.5 Analysis and synthesis

A thematic approach will be used to identify patterns in context, mechanisms, and outcomes first within each document and then across documents. To identify demi-regularities, attention will be given to similarities and differences in outcomes across different contextual factors. Specifically, we aim to identify those demi-regularities that might act as barriers or enablers to IDE participation. Through discussion with the research team, we will identify the mechanisms by which these outcomes occur. We will test the demi-regularities to see if they are able to confirm, refute, or refine our candidate theories. Other approaches to test and refine our theories include comparisons with published evaluations from other disciplines that have incorporated exercise into routine care, such as cardiology and pulmonary medicine. If the data does not fully explain candidate theories or new theories emerge from the data, we will develop these theories further by refocusing the literature search.

5.4 Discussion

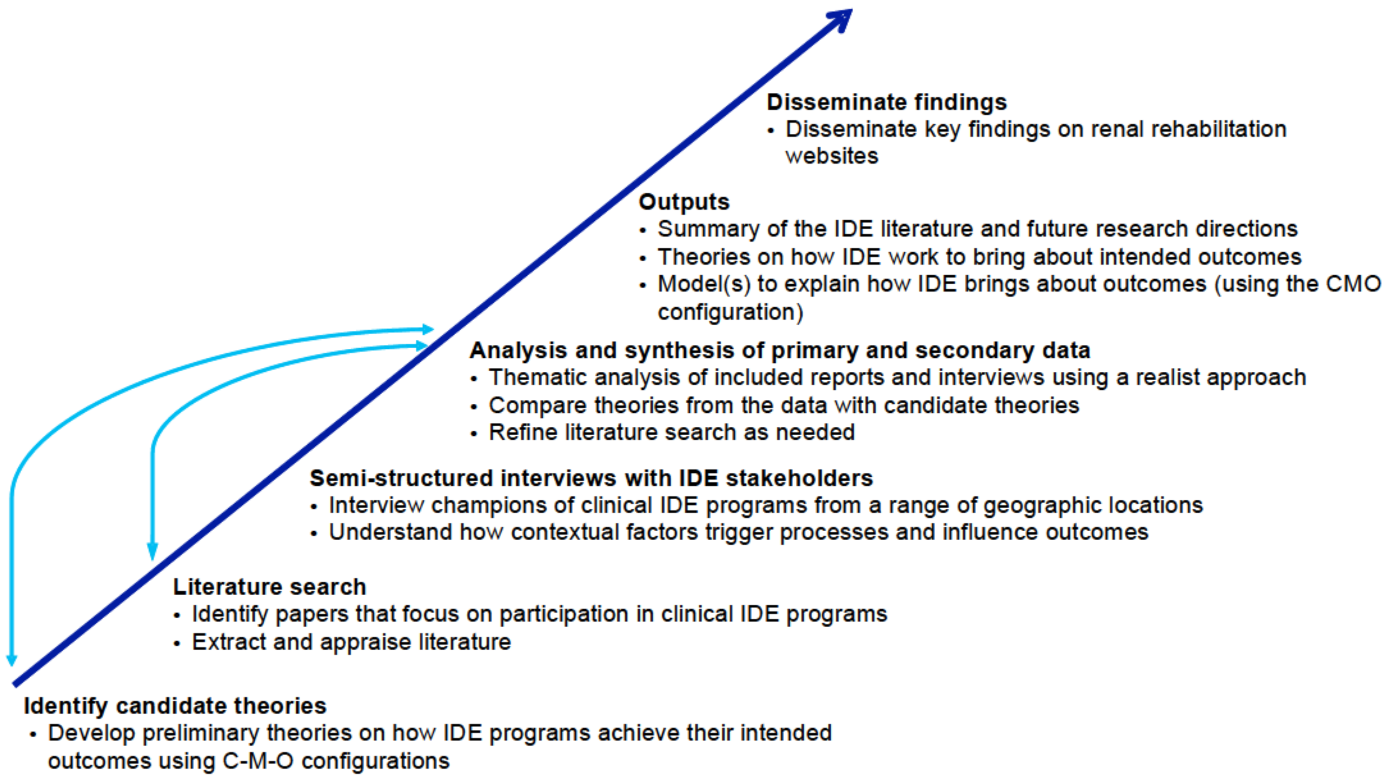
This realist synthesis aims to explain how contextual factors influence the mechanisms of IDE programs to effect patient participation. Previous reports of IDE interventions have primarily focused on the exercise itself and not considered how the more complex and variable aspects of an IDE program might influence its impact. To our knowledge, this will be the first report that explicitly defines intradialytic exercise as a complex intervention. This distinction is important and has implications for research utilization. Focusing on IDE mechanisms shifts the focus away from the problematic goal of delivering a complex intervention in a standardized way to understanding how the components of an IDE program function to bring about their outcomes and which of these mechanisms are important to reproduce.[13,17] How contextual factors modify the relation between mechanisms and outcomes is an additional advantage of the realist approach, as research users can understand how local resources may influence program impact.

One of the outputs from this review is a working model(s) that will explain the conditions for IDE program success. The model(s) will be constructed based on the CMO configuration, describing how different contextual factors work to influence the effectiveness of the IDE program.[18] All of the theories to describe how IDE programs work to increase patient participation will also be presented. Where possible, the theories generated from this review will be discussed alongside findings from systematic reviews on IDE and exercise chronic kidney disease.

The results of this review will be of interest to renal program administrators and a range of renal care providers. IDE programs are complex and potentially resource-intensive. Recommendations from this review on 'what works and under what circumstances,' will provide useful information to administrators on where and how to allocate resources so that the program is more likely to attain its intended health outcomes. Although renal care providers acknowledge the importance of physical activity for patients with kidney disease, implementation of practices to increase uptake are low.[21] Generalizable lessons that can be used to address recognized barriers to patient participation in IDE e.g., lack of unit staff's knowledge about IDE, difficulty motivating patients, and difficulty with existing resources, can improve the overall quality of IDE programs across a range of settings.[21–23]

The outputs will be disseminated through a number of different mechanisms. To provide guidance on implementation of IDE programs, the key findings of this review will be posted on the websites of the following renal organizations: Canadian Association of Nephrology Nurses and Technologists (CANNT), Kidney Foundation of Canada, and various renal rehabilitation websites internationally.

Figure 5-1. **Overview of the stages of the realist review.** The arrows indicate the iterative process of data collection, analysis, and theory development.



C-M-O=context-mechanism-outcome; IDE= intradialytic exercise

CHAPTER 6-OVERALL DISCUSSION AND CONCLUSIONS

6.0 Key findings

Chapter 3

In Chapter 3, an RCT and qualitative methods were used to rigorously evaluate the feasibility of an intradialytic exercise intervention of aerobic and resistance exercise. Feasibility of recruitment and high patient acceptability and adherence to the exercises was shown across all intervention groups. Low attrition and contamination during the trial suggests that blinding of staff and participants to study hypothesis and the use of an attention control were successful. These approaches to blinding were also practical to carryout. Patients' interactions with the kinesiologist facilitated acceptability of the attention control and in the active intervention groups, progression based on RPE and individual instruction were key to increasing exercise acceptability and adherence.

There was also an overall lack of readiness for IDE among unit staff, which had implications for patient recruitment, adherence, and the sustainability of the trial. Their lack of readiness was attributable to initial safety and workflow concerns with the exercise equipment, a lack of knowledge about the benefits of exercise in special populations, the heavy workload in the unit, poor integration of IDE into their workflow, and onerous trial data collection. For many unit staff, there was a lack of interest for education on IDE. However, seeing and hearing of the benefits of IDE first-hand from their own patients was an effective means of facilitating staff engagement.

For the secondary outcome of safety, of the approximate 900 training sessions that were performed, vascular access complications during exercise were exceedingly low and few participants experienced an episode of hypotension during the study period. Although approximately 50% of trial participants were diabetic, there were no hypoglycemic events during the study period. Furthermore, there was no clear relation between the higher volume of exercise in the combined group and the number of participants with AEs.

Chapter 4

To better understand the factors that influence IDE trial implementation, the concepts of key components unintended consequences were applied. One key component was the support of the kinesiologist, which functioned to enhance patients' confidence and sense of capability, thereby increasing patients' perceptions of program effectiveness. Delivering aspects of the IDE program in-keeping with unit norms, such as waiting until the dialysis-related tasks were complete before initiating IDE was another key component that served to increase staff acceptability of IDE. The staff's emphasis on patients setting-up their own equipment and enhanced social interaction among trial participants were additional themes that conveyed the unintended consequences of the intervention.

Other findings relevant to implementation were the discordant views on the role of the nurse in the delivery of IDE. Patients viewed IDE as consistent with the nurse's role as carer and as an advocate for what benefitted them. However, individual and system-level factors, such as personal beliefs about exercise, the prioritization of acute versus chronic issues, a lack of support from management, and an unawareness of the importance of their role as carer, were all potential factors that contributed to staff's view that provision of IDE was not their role. An additional theme of "no time" (for staff to participate in IDE) was influenced by its low priority in their workflow and the demands of the unit.

Chapter 5

Nine candidate theories have been developed for further testing (Table 6-1). From the initial search of the literature, 1,313 citations were identified and 101 articles potentially met inclusion criteria. A preliminary review of these articles shows that the relevance and rigor of the evidence is low, with a high number of experiential accounts of IDE programs and no information on program outputs or outcomes. Based on a sample from the included articles, potentially influential contextual factors at the individual level are: the technical expertise, leadership, dedicated time of the exercise specialist and the authority of the nephrologist in formalizing exercise as part of the treatment plan. Although staff's role in the IDE program is frequently described as 'crucial' or 'important,' it is typically not defined. Interpersonal factors include goal setting and performance-based feedback and assessment for patients. Including IDE in unit staff job descriptions and unit policies as well as staff evaluation and reward for IDE involvement were prominent institutional factors. Resources that were identified as important for IDE programs were equipment that is easy to move, visible, and designed for HD use. However, very few studies suggest how these contextual factors could trigger higher or lower patient participation and these factors were rarely linked to any outputs or processes. For example, Carlson et al.[1] proposed that allowing unit staff to make a decision to develop an exercise program would foster a sense of ownership and accountability for implementation; however, ownership and accountability are not linked with program outputs or outcomes. The interviews with IDE stakeholders are therefore critical to developing C-M-O configurations.

6.1 Importance of the findings

In order to meet the changing needs of care delivery and patient populations, identifying and filling knowledge gaps is a continual process within clinical research. Consequently, rather than justifying the continued underuse of exercise in people with ESRD, this work is intended to convey the strong therapeutic basis for exercise, to stimulate discussion on why we do not regularly endorse or provide exercise for our patients, and to suggest what can be done as researchers and clinicians to improve this.

6.1.1 Contribution to the literature and implications for research and practice

The practical value of identifying the optimal exercise prescription to address patient important outcomes is evident. Furthermore, the development of specific, evidence-based guidelines for people with ESRD requires the evaluation of different exercise prescriptions. Although the pilot RCT in this thesis does not allow for definitive conclusions on the efficacy or safety of different types of exercise, the study makes several valuable contributions to the literature. First, despite the low level of physical functioning, physical activity, and high comorbidity in this study population at baseline, exercise adherence and acceptability were high. As discussed in Section 2.3, commonly cited barriers to increasing physical activity in this population are a lack of motivation and the endorsement of too many medical problems. Our findings suggest that attributing low levels of physical activity in this population to these individual factors may be an oversimplification and that components of the exercise prescription and factors related to the setting and processes of IDE delivery can supersede individual level barriers. To identify the influence of contextual factors on exercise participation, it is important that investigators consider a broader approach to the evaluation of exercise behaviors. Second, this is one of very few exercise studies in people with ESRD where adverse events were rigorously evaluated and events that were relevant to patients and renal care providers and common to exercise training were identified a priori. Third, the effect of aerobic and resistance exercise each compared with control on QoL and physical function can be included in future meta-analyses. Fourth, greater flexibility in when exercise could safely be performed during the HD shift is of practical value to unit staff, exercise professionals, and patients; however, few trials have reported the hemodynamic effects of IDE. We showed that the BP response to exercise over the course of the exercise session was stable and that hypotensive events were infrequent overall. Finally, 'helping to pass the time' was a common benefit of IDE, which raises the possibility that some of the perceived improvement in wellbeing could be mediated through engagement in an activity, rather than exercise. For researchers, this finding has implications for IDE trial design and underscores the importance of using novel and rigorous methods of blinding—particularly when evaluating subjective outcomes.

This work is also the first to describe how staff readiness influenced trial implementation and to propose strategies to address these barriers. Although education and policy development are common approaches to integrating change into the healthcare system,[2] these are not effective means of changing attitudes and beliefs—particularly if there is a lack of willingness to engage with the topic. In this setting, we found that providing staff with the opportunity to become familiar with IDE and to hear the benefits of IDE first-hand from their patients is one potential means of improving preparedness. This finding is unsurprising given the professional emphasis on practical knowledge and busyness[3,4] and the staff's perceived time constraints and workload. Furthermore, these demands have been reported in other studies on care delivery in the dialysis unit suggesting that this approach may be successful across a number of settings.[4,5] Patients' perceptions that the more physically active nurses were more involved in IDE delivery is new. For renal program administrators implementing IDE programs, concurrent exercise initiatives for staff could serve to identify exercise as a priority within the renal organization, thereby increasing staff's motivation and preparedness for IDE.

Our findings suggest that incorporating social support into IDE interventions could increase their effectiveness. Focusing on the function of the key component (enhancing patients' confidence and sense of capability) rather that its form (an exercise professional) is an important distinction to make for research users.[6] Renal programs may not have the resources for an exercise specialist but could assign the role of providing emotional support to another health professional. Delivering IDE within the unit's norms is also a transferable lesson and underscores the importance of understanding what behaviors are valued within the unit prior to implementation.

The function of key components is analogous to the realist description of mechanisms in Chapter 5. Understanding the influence of varying contextual factors on patient participation in IDE will provide more generalizable findings for renal program administrators. For example, the support of the exercise specialist may work to increase patient participation through enhancing patients' confidence and sense of capability in programs that use goal setting but not in programs that do not use any form of feedback and assessment on patients' exercise goals. Similarly, delivering IDE in keeping with unit norms may only influence patient participation in dialysis units that are understaffed.

Exercise can promote social inclusion and engagement by enhancing and supporting opportunities for social interaction.[7] We showed that increased social interaction was a positive aspect of IDE participation and could serve as a means of increasing program reach. Of interest to renal program administrators, this benefit could also improve patients' satisfaction with care. Moreover, patient participation in IDE programs may be increased with a greater focus on group-based exercise.

6.2 Strengths and limitations

To our knowledge, this work is the first to evaluate the design of an IDE trial using a mixed methods approach. The qualitative data was critical in identifying barriers to trial implementation and to understanding how the intervention could be refined. For several of the findings presented in Chapter 3, it would have been informative to triangulate the qualitative and quantitative data. For example, comparing patients' experiences of various program factors by high or low adherence may be useful. However, this type of analysis was limited by the small sample size. In addition, the focus of Chapters 3 and 4 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.

The trial study population was small and relatively homogeneous with respect to sex, age, and ethnicity. Therefore, participant experiences according to these characteristics was not explored. Additionally, the findings from Chapters 3 and 4 were from a single HD unit and differences in contextual factors may influence the transferability of the findings. Although the intent of qualitative research is not to generalize findings to the wider population, it is likely that the themes and issues presented in this work will have relevance and/or will be recognizable to the reader. First, several of the findings were consistent with those described in reports from different settings.[8–10] Second, the focus was on identifying key components (Chapter 4), which facilitates the transferability of the findings. Third, where previous qualitative studies have primarily been descriptive, the methodology (interpretive description) used in this study is aimed at discovering relationships and patterns that can be integrated into useable knowledge.

Many of the issues discussed in Chapters 3 and 4 highlight the challenges for modern nephrology that were described in Section 2.5 (i.e. the incompatibility between how HD care is delivered and the increasing frailty and physical impairment of the average HD patient). Therefore, by contextualizing our findings within current issues in HD care, this work improves our understanding of the existing barriers to chronic disease management in the dialysis unit.

The realist synthesis will contribute to a growing field of knowledge synthesis for complex interventions. This study is also the first to apply this line of inquiry to the evaluation of exercise programs in people with kidney disease. The sampling plan for this study has yielded a heterogeneous group of IDE programs and will facilitate the construction of generalizable lessons on 'what works and under what circumstances,' thus extending the relevance of this work to a broad audience of IDE stakeholders. In addition, insight into how contextual factors work to bring about a program's intended outcomes may generate hypotheses about why systematic reviews have reported inconsistent findings for specific outcomes, such as QoL. As with all types of knowledge syntheses, the results are only as good as the supporting data. Therefore, given the limited data on mechanisms and outcomes in the published literature, testing of the candidate theories will rely heavily on interview data and it is possible that all candidate theories cannot be tested. Finally, the aim of this study is to understand the broad range of contextual factors affecting patient participation in exercise. Therefore, patients' perceptions on IDE participation will not be fully captured.

6.3 Future directions

Based on the current exercise literature in people with ESRD and from the findings presented in this thesis, to increase the clinical uptake of IDE, future research should focus on understanding how to increase the effectiveness, adoption, and sustainability of IDE. This focus is consistent with our role as clinicians: to know how to optimally treat disease and to relieve symptoms.

Accomplishing these complimentary aims requires a better understanding of the mechanisms that underlie exercise intolerance and how to promote exercise participation for people with ESRD in a way that is consistent with patient needs and that is feasible for systems and clinicians to support. Specific questions related to these remaining knowledge gaps and the priority with which they should be addressed is shown in Figure 6-1.

6.3.1 Increasing the effectiveness of exercise interventions for people with CKD

A known challenge for researchers designing exercise RCTs in people with ESRD is the heterogeneity in the clinical characteristics of participants.[11] This heterogeneity is one potential explanation for some of the negative or more modest effects of exercise trials. As a 'one size fits all approach' to exercise may not be an effective approach to improving health outcomes in people with ESRD, more targeted exercise interventions are required. Designing and targeting interventions requires knowledge of the sociodemographic, physiological, and psychological mechanisms that underlie the outcomes of interest. For example, there are many potential mediators of the effect of exercise on quality of life (e.g., decreased fatigue, increased strength, increased social interaction, improved self-efficacy and mastery). Identifying the factor(s) that mediate the association between exercise and QoL suggests that exercise interventions should also target this outcome. Knowledge of these mediators would also improve our understanding of patients' differential responses to exercise. Furthermore, understanding how exercise mediates its effect on specific outcomes serves to identify potential targets for other interventions that could be used singly or in conjunction with exercise to improve outcomes in people with ESRD.

Information from large prospective observational studies of people with advanced CKD could also inform the development of exercise interventions. Information on physical, physiological, and behavioral variables could be used to test specific hypotheses on clinically important outcomes such as mortality, hospitalization, and quality of life. The data collected from this cohort could also be used to identify the optimal time to implement exercise interventions in the disease course of CKD and what groups would benefit from early intensive interventions.

6.3.2 Increasing the adoption and sustainability of exercise in nephrology practice

Increasing the relevance of IDE research for health care providers, renal program administrators, and patients could improve the adoption and sustainability of exercise in practice. One means of accomplishing this is by including these perspectives in the identification of research priorities.[12,13] Applying the findings from one study that explored research priorities for nephrology with patients suggests that future exercise trials should evaluate disease specific outcomes, such as fatigue and cramping.[14] However, more of these types of studies are needed in order to understand those questions specific to exercise. Investigators should also consider the significance of their selected outcomes within the context of HD care. For example, the knowledge that exercise improves aerobic capacity in ESRD is important, but for clinicians and patients this finding has greater relevance if improvements in fitness translate to decreased symptom burden e.g. breathlessness and fatigue.

Of note, patients and caregivers in one study[14] identified the following question as a research priority: what is the effect of exercise on a dialysis patient's health? This question is not surprising given what is known about the low counseling practices among renal health professionals[15–17] and underscores the need for practical and effective exercise education for patients and providers. More research is needed to extend our understanding of renal health professionals' influence on patients' exercise knowledge and behavior and to determine what strategies are associated with increased exercise participation and how this could be feasibly accomplished in practice.

Although exercise trials in people with ESRD have included patient reported outcomes (primarily QoL), exercise research in ESRD has not been patient centered. For example, little is known about the exercise preferences of people with ESRD or how patients would like to receive information on physical activity and exercise (though this information has clear implications for participation and adherence). In addition, the perspectives of renal program administration on IDE have not been extensively explored but are critical to understand. Ultimately, it is the implementation and eventual institutionalization of exercise policies in the unit that will lead to IDE becoming a part of the culture of the unit.

Finally, a critical research gap in the uptake of IDE into practice is the cost-effectiveness of these programs. Although a cost evaluation of IDE is beyond the scope of this thesis, it remains an important issue for HD program administrators. Based on an analysis of data from the United States Renal Data System, cardiac rehabilitation post coronary artery bypass grafting was associated with a highly cost-effective incremental cost effectiveness ratio.[18] However, to date, the cost effectiveness of a renal exercise program has not been evaluated in people with kidney disease.

6.3.3 Future directions for policy development

To prioritize exercise promotion in HD care, clear support for exercise in people with ESRD must be demonstrated at the policy level. This includes more specific instructions from K/DQOI on how exercise participation can be promoted. Effective translation of guidelines requires more than the vague advice to encourage patients to do more, a little more often. In addition, wellness initiatives, such as IDE have largely been absent from pay for performance plans and quality improvement initiatives. These system level approaches to increase the uptake of IDE are justifiable based on the potential for benefit, apparent safety, and patient demand for exercise.

Using outcomes that are patient centered (e.g. decreasing treatment-related symptoms, patient satisfaction, social interaction) to evaluate these programs adds relevance and implicit value to IDE programs and could provide the impetus for a broader and more patient centered set of quality of care indicators for HD delivery. From a practical perspective, what form of exercise promotion is implemented could be determined at the renal program level based on patient priorities and unit resources.

For nephrologists, it is important to recognize that professional roles need to evolve with the needs of patients and systems. Yet, exercise in people with kidney disease is a topic missing from the agendas of influential physician-led organizations (The Canadian and American Societies of Nephrology). These societies help define the scope of nephrology practice and through supporting the development of curricula and practice tools on exercise in ESRD, are well positioned to endorse the nephrologist's role in exercise delivery.

6.4 Knowledge translation strategy

This work has had an immediate local impact and will provide researchers and clinicians from other renal programs with guidance for IDE implementation. The knowledge translation (KT) strategy for local activities within the Northern Alberta Renal Program (NARP) is shown in Table 6-2 and at the national and international level in Table 6-3.

In collaboration with local administration, the findings from Chapters 3 and 4 were used to inform the implementation of NARP's first clinical IDE program. Approximately 45% of the patients in this unit (n=110) are participating in the IDE program. This is currently NARP's only IDE program; however, there is demand for IDE from patients and managers in other units. The IDE program has been included in NARP's strategic plan and in collaboration with NARP administration, dialysis unit staff, and the local chapter of the Kidney Foundation, expansion of the program to other sites is planned. To inform the process of scaling up IDE, key findings from Chapters 3-5 will be applied. In particular, the findings from Chapter 5 will be used to guide expansion of the IDE program across the varied settings and resources of the satellite HD units in northern Alberta.

6.5 Conclusions

This thesis contributes useful knowledge to the IDE literature on how key methodological and practical limitations could be feasibly improved in order to increase trial quality, relevance, and potentially effectiveness. A mixed methodological approach facilitated identification and improved understanding of the broad range of factors that renal program administrators, health care providers, and researchers should consider in the implementation of IDE. Importantly, this work expands the purely technical focus of current exercise trials to show the importance of these largely modifiable contextual influences.

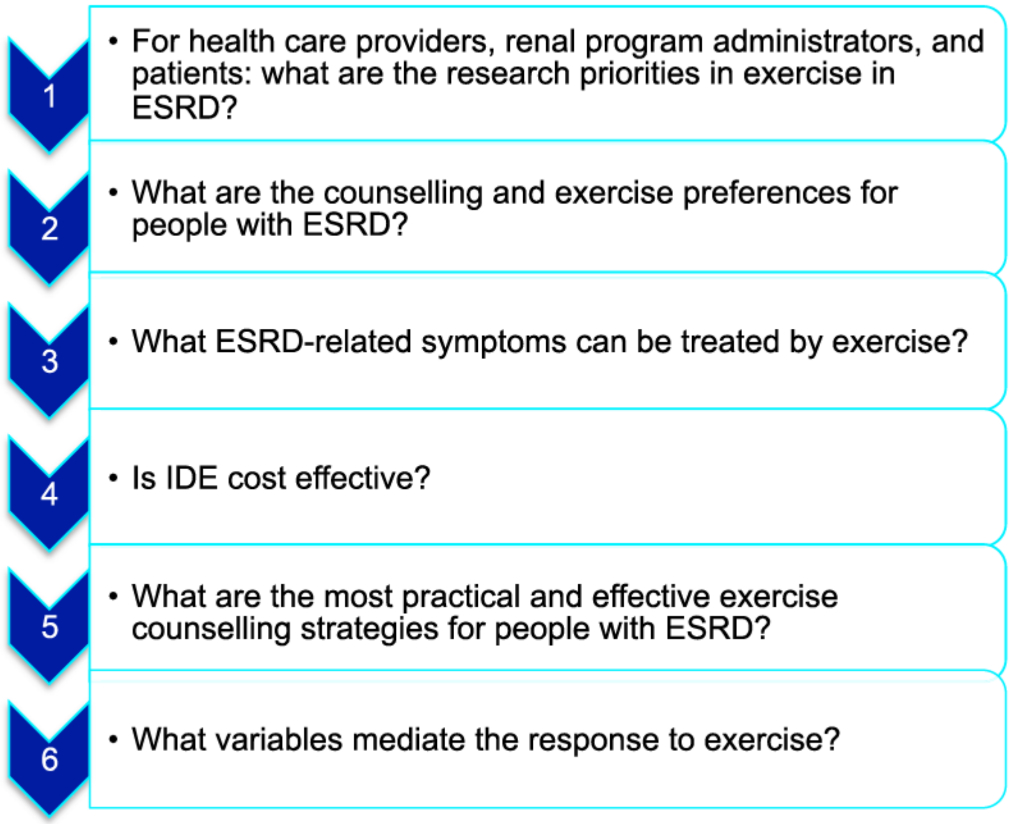
Table 6-1. Initial candidate theories for the realist synthesis

Basis & source	Level of contextual factor	Contextual factor	Mechanism	Configuration
1. Social cognitive theory	Individuals	Exercise professional (EP)	EP involvement increases patients' self efficacy (confidence patients have in their ability to exercise)	IDE programs with EPs increase patient participation in IDE through increasing patients' self-efficacy through any of the following aspects of self efficacy: enhancing body knowledge, body confidence, using verbal persuasion, feedback
2. Social cognitive theory Thompson et al. 2016[40]	Individuals	Unit staff /EP involvement	Increases social support (SCT)	IDE programs increase patient participation in IDE by promoting social support which imparts a sense of esteem to participants
3. Clark et al. 2005[65]	Individuals	Individuals & Lines of communicatio n	Social camaraderie and/or social capital is enhanced through performing a common activity or by altering subjective norms	Participation in IDE is reinforced through performing a common activity, which serves to enhance camaraderie and/or social capital
4. Theory of planned behavior Bennett at al. 2010[66]	Individuals	Medical staff (nurse/physici an) involvement in the implementatio n or day-day delivery of the program	Alters normative beliefs about what behaviors are valued during the dialysis shift e.g. exercise culture (TPB: subjective norms & normative beliefs inform intention [readiness to perform behavior]).	A program where those who deliver IDE are also those who deliver/oversee medical care increases patient participation through reinforcing normative beliefs about the value of IDE.

5. Social cognitive theory	Lines of communication	Goal setting between participant and EP (or staff)	Outcome expectancy (increases belief that exercise will lead to a certain outcome)	Patient participation is increased in with structured assessments and feedback through promoting the belief that exercise will lead to a defined outcome
6. Social cognitive theory Expert opinion	Individuals	Modeling i.e. other people exercising on the shift	Observational learning results from seeing other patients exercise (other patients perceived as 'credible' role models')	Patient participation in IDE is increased through observational learning: seeing other patients exercise during the shift
7. Social cognitive theory Bayliss 2006[67]	Resources	Individualized program plans; varied equipment	Exercise tailored to the patient's preference and ability leads to greater self-efficacy and minimized socio-structural barriers	By minimizing socio-structural barriers and tailoring exercise to preferences and ability, participants have greater self efficacy in their ability to perform exercise
8. Transtheoretical stages of change Bayliss 2006[67]	Institution	IDE is included in job descriptions and unit policies	These policies re-structure the dialysis unit environment to have reminders and cues that support and encourage the healthy behavior (stimulus control)	Patient participation is increased through structural cues for patients and staff
9. Theory of reasoned action Pentecost & Taket[68]	Individuals & Lines of communication	Exercise is in a group setting	Social pressure and personal attitude	Participation in IDE is increased by seeing other patients exercise and perceiving them to be similar

IDE=intradialytic exercise

Figure 6-1. Remaining key knowledge gaps for IDE in order of priority



IDE=intradialytic exercise

Table 6-2. Local knowledge translation strategy (NARP)

Objective	Audience	Strategy and collaborations
To increase knowledge and awareness of the benefits of exercise for people with ESRD	Renal program administration	Presented summary of key findings to local HD unit program administration
	HD unit staff	Presented preliminary study findings to unit staff at the participating site. Suggestions sought for clinical program implementation.
	Nursing and allied health in NARP	Presented study findings, educational information on IDE, and delivered a brief exercise session on unit-friendly exercises for staff at NARP's program-wide nurse education day
	Nephrologists, nursing, allied health, management	Presented study findings at city wide nephrology rounds in Edmonton (University of Alberta) and Calgary (University of Calgary)
	General public Industry groups and funders	In collaboration with the local chapter of the Kidney Foundation of Canada, increase awareness via social media and media releases (CTV & global television Edmonton)
To inform policy and change practice	Renal program administration and dialysis unit staff	Delivered key messages relevant to the implementation of the clinical IDE program (e.g. evaluating unit staff readiness and workflow; role of unit staff and kinesiologist) In collaboration with the kinesiologist, unit management and volunteer nursing staff: • Added an exercise section to HD unit charts and to daily HD run sheets • Developed a promotional video for IDE • Conducted staff and patient wellness challenges in the unit In progress • Developing in-servicing tools for IDE

		programs at other sites • Engaging nurse champions at other HD units in NARP to take a lead role in implementing IDE programs • Forming an IDE program advisory committee to oversee program development at each site (representation from unit staff, administration, and patients).

IDE=intradialytic exercise; HD=hemodialysis; NARP=Northern Alberta Renal Program

Table 6-3. Knowledge translation strategy (national and international audience)

Objective	Audience	Strategy and collaborations
To inform future research	Researchers, clinicians, allied health	Presented findings from chapter 4 at the Canadian Society of Nephrology annual general meeting Chapter 3 journal submission plan: Implementation Science (open access) Chapter 4 accepted for publication with the Clinical Journal of the American Society of Nephrology (February 23, 2016) Chapter 5 accepted publication Systematic Reviews (open access; February 24, 2016)
To inform policy and change practice	Researchers, renal health care professionals, patients	Using pre-existing networks in Canadian IDE programs (Calgary and Winnipeg) and networks developed through interviews with stakeholders on a national scale (chapter 5) to develop practice communities. Web-based collaborations will be used to share evidence and understand barriers/facilitators to the use of findings
	Renal program administration, renal health care professionals	Disseminate generalizable lessons from chapter 5 on the websites of the Canadian association of Nephrology Nurses and Technologists, National Kidney Foundation, and various renal rehabilitation websites world-wide

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APPENDIX-1

Appendix 1: Electronic search strategies

Search dates: May 1, 2010-January 30, 2016

DATABASE

<u>CENTRAL</u>

1. renal dialysis/ or hemofiltration/ or hemodiafiltration/
2. (hemodialysis or haemodialysis or dialysis or renal replacement therapy) ti,ab.
3. Renal Replacement Therapy/
4. 1 or 2 or 3
5. exp Exercise/
6. exercise movement techniques/ or exp exercise therapy/
7. Weight Lifting/
8. (exercis* or aerobic* or training or physical activit* or fitness or weightlifting or weight lifting or physical therapy or physical exertion).ti,ab.
9. Physical Exertion/
10. Physical Therapy Modalities/
11. physical endurance/ or bicycling/ or running/ or jogging/
12. or/5-11
13. 4 and 12

<u>EMBASE</u>

1. exp hemodialysis/ or exp renal replacement therapy/
2. hemodialysis patient/
3. dialysis/
4. (hemodialysis or haemodialysis or dialysis or renal replacement therapy).ti,ab.
5. 1 or 2 or 3 or 4
6. "physical activity, capacity and performance"/ or endurance/ or exp exercise/ or exercise recovery/ or training/
7. exp treadmill exercise/ or exp exercise recovery/ or exp leg exercise/ or exp exercise tolerance/
8. physical activity/ or cycling/ or jogging/ or running/ or swimming/ or weight bearing/ or weight lifting/
9. kinesiotherapy/ or arm exercise/ or dynamic exercise/ or exercise recovery/ or isokinetic exercise/ or isometric exercise/ or movement therapy/ or muscle training/ or plyometrics/ or static exercise/ or stretching exercise/
10. exp muscle strength/
11. exp physiotherapy/
12. (exercis* or physical activit* or fitness or weightlifting or weight lifting or strength training or resistance training or physical therapy or physical exertion).mp.
13. or/6-12
14. 5 and 13
15. exp clinical trial/
16. randomi?ed.ti,ab.
17. placebo.ti,ab.

18. dt.fs.
19. randomly.ti,ab.
20. trial.ti,ab.
21. groups.ti,ab.
22. or/15-21
23. (exp vertebrate/ or animal/ or exp experimental animal/ or nonhuman/ or animal.hw.) not (exp human/ or human experiment/)
24. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. not (exp human/ or human experiment/)
25. 23 or 24
26. 22 not 25
27. 14 and 26
28. limit 27 to english language
29. limit 28 to (conference abstract or editorial or letter or note)
30. 28 not 29

<u>Medline</u>

1. renal dialysis/ or hemofiltration/ or hemodiafiltration/
2. (hemodialysis or haemodialysis or dialysis or renal replacement therapy).mp.
3. Renal Replacement Therapy/
4. 1 or 2 or 3
5. exp Exercise/
6. exercise movement techniques/ or exp exercise therapy/
7. Weight Lifting/
8. (exercis* or aerobic* or training or physical activit* or fitness or weightlifting or weight lifting or physical therapy or physical exertion).mp.
9. Physical Exertion/
10. Physical Therapy Modalities/
11. physical endurance/ or bicycling/ or running/ or jogging/
12. or/5-11
13. 4 and 12
14. randomized controlled trial.pt.
15. clinical trial.pt.
16. randomi?ed.ti,ab.
17. placebo.ti,ab.
18. dt.fs.
19. randomly.ti,ab.
20. trial.ti,ab.
21. groups.ti,ab.
22. or/14-21
23. animals/
24. humans/
25. 23 not (23 and 24)
26. 22 not 25
27. 13 and 26
28. limit 27 to (case reports or comment or editorial or news)

29. 27 not 28
30. limit 29 to english language

APPENDIX-2

Search results (RCTs only)

1. A nurse-led case management program on home exercise training for hemodialysis patients: A randomized controlled trial. Int J Nurs Stud. 2015 01 Jun 2015;52(6):1029-41.
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3. Aerobic or Resistance Training and Pulse Wave Velocity in Kidney Transplant Recipients: A 12-Week Pilot Randomized Controlled Trial (the Exercise in Renal Transplant [ExeRT] Trial). Am J Kidney Dis. 2015 01 Oct 2015;66(4):689-98.
4. Combination of exercise training and dopamine agonists in patients with RLS on dialysis: A randomized, double-blind placebo-controlled study. ASAIO Journal. 2015 03 Nov 2015;61(6):738-41.
5. Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. Int Urol Nephrol. 2015 01 Feb 2015;47(2):359-67.
6. Effect of chair stand exercise on activity of daily living: a randomized controlled trial in hemodialysis patients. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2015 01 Jan 2015;25(1):17-24.
7. Intra-dialytic training accelerates oxygen uptake kinetics in hemodialysis patients. European Journal of Preventive Cardiology. 2015 09 Jul 2015;22(7):912-9.
8. Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: A pilot randomized controlled trial. American Journal of Kidney Diseases. 2015 01 Mar 2015;65(3):425-34.
9. Effect of intradialytic exercise on echocardiographic findings in hemodialysis patients. Iranian Journal of Kidney Diseases. 2014 2014;8(3):207-11.
10. Effects of intradialytic cycling compared with pedometry on physical function in chronic outpatient hemodialysis: a prospective randomized trial. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association European Renal Association. 2014 01 Oct 2014;29(10):1947-55.
11. Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. Int Urol Nephrol. 2014 2014;47(2):359-67.
12. Effect of individualized exercise during maintenance haemodialysis on exercise capacity and health-related quality of life in patients with uraemia. J Int Med Res. 2014 June 2014;42(3):718-27.

13. Aerobic exercise increases phosphate removal during hemodialysis: A controlled trial. Hemodialysis International. 2014 April 2014;18(2):450-8.

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21. Effect of peripheral and respiratory muscle training on the functional capacity of hemodialysis patients. Ren Fail. 2013 March 2013;35(2):189-97.

22. Effect of intradialytic aerobic exercise on serum electrolytes levels in hemodialysis patients. Iranian Journal of Kidney Diseases. 2012 March 2012;6(2):119-23.

23. Intra-dialytic electrostimulation of leg extensors may improve exercise tolerance and quality of life in hemodialyzed patients. Artif Organs. 2012 January 2012;36(1):71-8.

24. Combined resistance and aerobic exercise is better than resistance training alone to improve functional performance of haemodialysis patients - Results of a randomized controlled trial. Physiotherapy Research International. 2012 December 2012;17(4):235-43.

25. Effects of physical exercise on life quality of kidney transplant recipients. Chinese Journal of Tissue Engineering Research. 2012 2012;16(31):5733-6.

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