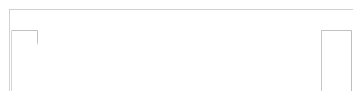


**Effect of an Exercise Rehabilitation Program on Symptom Burden
and Quality of Life in Hemodialysis: A Randomized Controlled Trial**



NCT02259413

RENAL REHAB PROTOCOL

EFFECT OF AN EXERCISE REHABILITATION PROGRAM ON SYMPTOM BURDEN IN HEMODIALYSIS: A RANDOMIZED CONTROLLED STUDY

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The information within this document is confidential and is not to be disclosed without prior permission of the Study Principal Investigator.

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STATEMENT OF COMPLIANCE

Protocol: The Effect of an Exercise Rehabilitation Program on Symptom Burden in Hemodialysis: a Randomized Controlled Study	Version/Date: Version 4, 15 Oct 2018
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Study Principal Investigator: Clara Bohm, MD, MPH

Site: University of Manitoba

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in Health Canada's section C.05.010/Division 5 of the Food and Drug Regulations and the International Conference on Harmonization (ICH) document E6 Good Clinical Practices: Consolidated Guidance. As the Site Principal Investigator, I agree to conduct and carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the Study Principal Investigator and approval from the Research Ethic's Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection training.

Principal Investigator (Print)

Principal Investigator (Signature)

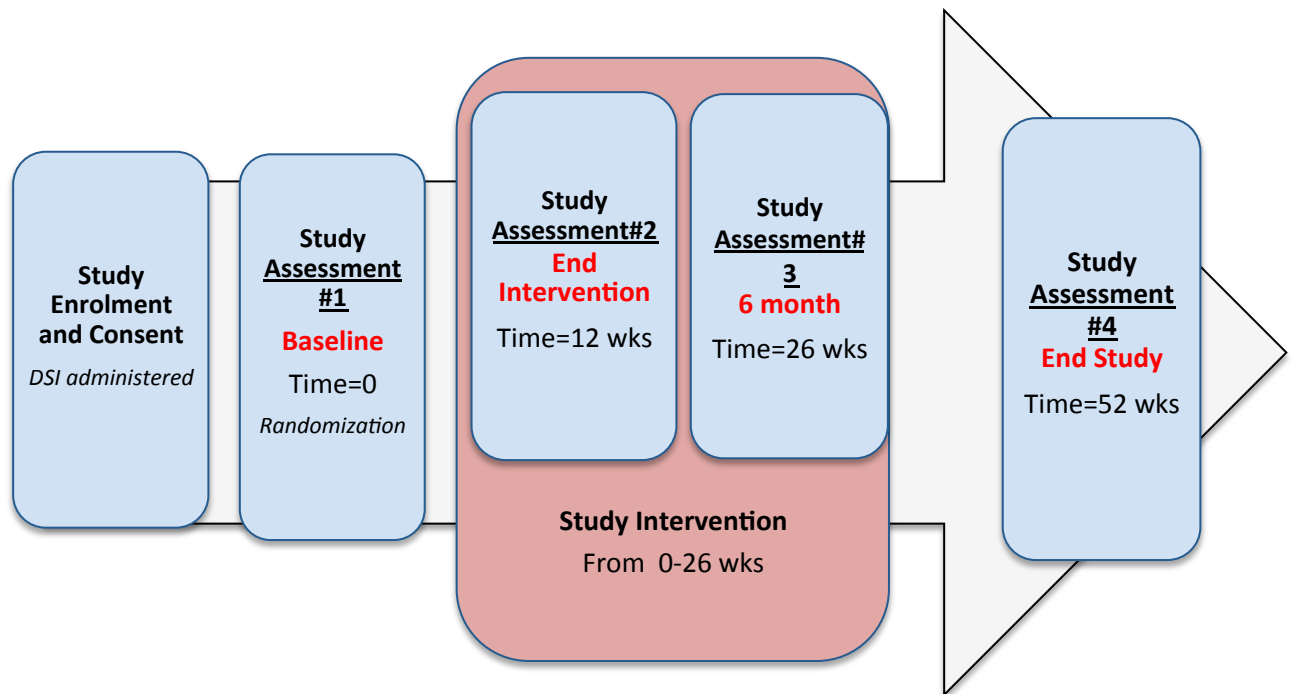
Date

PROTOCOL SYNOPSIS

Title & Protocol #	The Effect of an Exercise Rehabilitation Program on Symptom Burden in Hemodialysis: a Randomized Controlled Study
Sponsor	University of Manitoba
Investigators and Sites	Study PI: Clara Bohm, MD, MPH (Winnipeg); co-PI: Jennifer MacRae MD, MSc (Calgary); co-Invest: Todd Duhamel, PhD (Winnipeg); Mauro Verrelli, MD (Winnipeg); Claudio Rigatto MD, MSc (Winnipeg); James Zacharias, MD, MSc (Winnipeg); Navdeep Tangri MD, PhD (Winnipeg)
Objectives	<p>Primary: To characterize the effect of a 26-week exercise rehabilitation program on symptom burden at 12, 26 and 52 weeks in adults on hemodialysis (HD)</p> <p>Secondary: To characterize the effect of a 26-week exercise rehabilitation program on:</p> <ul style="list-style-type: none"> - Symptom burden at 52 weeks in adults on HD - Generic health related quality of life at 12, 26 and 52 weeks in adults on HD <p>Tertiary: To determine the effect of a 26-week exercise rehabilitation program on:</p> <ul style="list-style-type: none"> - Self-reported time required for recovery post hemodialysis at 12, 26, and 52 weeks - Physical activity behavior at 12, 26, and 52 weeks - Exercise capacity at 12, 26 and 52 weeks - Frailty status at 12, 26, and 52 weeks - Self-efficacy to exercise at 12, 26, and 52 weeks - Hospitalization rate over 1 year and hospital length of stay - Mortality at 1 year
Duration	4 years
Population	Adults on chronic in-centre hemodialysis for greater than 3 months with at least one hemodialysis-related symptom will be enrolled (n=150).
Design	Single centre randomized controlled trial with 1-to-1 parallel design, allocation concealment and assessor blinding.
Inclusion / Exclusion Criteria	<p>Inclusion Criteria: Participants must be able to understand and provide written informed consent in English; greater than or equal to 18 years old; greater than 3 months after starting chronic HD; no expected change in dialysis modality or relocation outside of Winnipeg during intervention period (26 weeks); assessed to be safe and able to exercise by HD unit nephrologist;</p> <p>Exclusion Criteria: acute coronary syndrome in past 3 months; unstable arrhythmia; shortness of breath at rest or with minimal activity (NYHA Class 4); symptomatic hypoglycemia (> 2x/week in week prior to enrolment); currently participating in the MRP clinical intradialytic cycling program; score of 0 on DSI when administered at time of consent</p>
Study Arms	<p>Intervention arm: Standard care plus a 26 week structured rehabilitation program including lifestyle education, home-based resistance exercise and cycling during HD; n=75</p> <p>Control arm: Standard care including baseline exercise counseling; n=75</p>
Study Endpoints Primary, Secondary and Mechanistic	<p>Primary outcome: Change in symptom burden over time (12, 26, 52 weeks) as measured by Dialysis Symptom Index (DSI) severity score.</p> <p>Secondary outcomes: Change in generic health-related quality of life over time (12, 26, 52 weeks) as measured by EuroQol 5D-5L and EuroQol visual analogue scale</p> <p>Change in: modified symptom burden (modified DSI severity score); time for recovery post-HD; frailty status (Fried criteria); physical activity level (accelerometer and Godin-Shephard Leisure Time Physical Activity Questionnaire); exercise capacity (Incremental Shuttle Walk Test); self-efficacy for exercise (Self-Efficacy for Exercise Questionnaire); hospitalization rate (number hospital</p>

	days admitted/patient year); all cause 1 year mortality
Brief Summary of Analysis	<p>Sample size: The following assumptions were made: alpha 0.05; power 0.80; 30% dropout and 25% absolute difference in proportion of individuals in whom DSI severity score decreases by 7 points or more (minimal clinically important difference). Therefore, assuming a baseline symptom prevalence of 50% of individuals in each study group, 150 patients (75 in each arm) will be randomized and we will be able to detect a 25% reduction in the primary outcome.</p> <p>Primary analysis: Intention-to-treat, available-case basis, in the intervention versus control arm, using Chi-square test and logistic regression for categorical outcomes and t-tests/MannWhitney U for continuous outcomes.</p> <p>Secondary outcomes: Descriptive statistics, Kaplan Meier analysis, Poisson regression and linear mixed modeling and will be used as appropriate.</p>

SCHEMATIC OF THE STUDY DESIGN



Enrolment and consent: Once informed consent is obtained, the Dialysis Symptom Index (DSI) will be administered to all participants. Those who score 0 on the DSI (no symptoms) will be deemed ineligible for the study

Randomization: To avoid bias, randomization will be performed following the baseline assessment.

Intervention phase: Participants in “intervention” group will receive study intervention during this time.

1 KEY ROLES

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2 INTRODUCTION, BACKGROUND INFORMATION AND RATIONALE

2.1 Background information

Individuals with end-stage kidney disease (ESKD) require renal replacement therapy such as hemodialysis (HD), peritoneal dialysis, or renal transplantation to sustain life. In Canada, the majority (76%) of the 5500 individuals who enter this stage of kidney disease annually start in-centre HD.¹ Individuals on HD are known to have low self-reported functional status, and poor health-related quality of life (HRQOL) when compared to general population controls.^{2, 3} Functional status is an important component of HRQOL and refers to the ability to perform activities required for daily life.

Symptom burden, the combined impact of the number and severity of symptoms experienced by an individual, is high in HD and contributes to poor functional status and HRQOL. Cross-sectional studies show that 30-80% of individuals on HD have at least one symptom that is related to ESKD or dialysis treatment, with a mean of 6-20 symptoms endorsed per individual.⁴⁻⁸ In a systematic review of symptom burden in chronic kidney disease (CKD), fatigue was identified as the most widespread symptom, with a weighted mean prevalence of 81%.⁵ Frequent symptoms (>50% prevalence) also included lack of sleep, pain, muscle cramping, pruritus (itch), decreased appetite, drowsiness and dry skin.^{5, 9} Other symptoms identified in more than 30% of patients include restless legs syndrome, difficulty concentrating, anxiety and depression.^{4, 5, 10}

Increased physical activity through exercise programming may play a role in symptom control. Increased prevalence of symptoms is correlated with low physical activity in individuals on dialysis.^{11, 12} Even in low functioning HD patients, exercise programming has been shown to be safe and to improve outcomes closely associated with symptom burden, such as functional status and HRQOL.^{13, 14} As well, several small randomized controlled trials (RCTs) have demonstrated improvement in specific individual HD-related symptoms such as restless legs and insomnia.¹⁵⁻²⁵ Using RCT methodology, we aim to characterize the role of exercise rehabilitation in managing symptom burden in chronic HD to determine if such a program can ameliorate common symptoms like insomnia, pain and fatigue, resulting in improved quality of life and reduced disability over the long term.

2.1.1 HD-related symptoms are a research priority

Multiple studies have shown that symptom burden in individuals on HD is similar to those living with metastatic cancer.⁵ HD therapy itself does little to improve symptom burden and may worsen symptoms. In a study of 698 hemodialysis patients followed for 1 year after starting HD, symptoms worsened in 23%, did not change in 56% and improved in only 19% of patients over the first year on HD.²⁶ Furthermore, healthcare providers have limited awareness of the presence and severity of symptoms in patients on HD. When responses to the Dialysis Symptom Index (DSI) were compared between 75 HD patients and 18 providers (nephrologists, nurse practitioners, physician assistants and nurse managers), providers underreported 97% of symptoms and underestimated symptom severity in 63%.⁴ Even when recognized, limited effective treatments exist for

most symptoms. For those few symptoms for which there are effective pharmacological therapies (uremic pruritus, restless legs syndrome, and depression), patients may be hesitant to take additional medications due to pre-existing medication burden (median of 19 medications per day) or attribution of symptoms to acute events.²⁷⁻²⁹

Most importantly, the identification of effective treatments for HD-related symptoms has been identified as an important knowledge gap for HD patients and their caregivers. Using methodology established by the James Lind Alliance, patients, caregivers and healthcare providers from across Canada identified the improvement of symptom burden and quality of life as research priorities for individuals at or nearing dialysis.³⁰ Using similar methodology, international groups have identified fatigue/energy, sleep, anxiety/stress and decreased appetite as key outcomes to be assessed in any future research studies.^{31, 32}

2.1.2 Exercise programming may play a role in symptom control

Low physical activity is correlated with increased prevalence of symptoms in individuals on dialysis.^{11, 12} In an observational study of 1643 incident dialysis patients, each 10-point increase in self-reported physical activity level measured using the Human Activity Profile was associated with a 20% decrease in symptoms of insomnia and restless legs and a 37% decrease in symptoms of depression.¹²

Evidence from small RCTs suggests that exercise can improve specific HD-related symptoms. In two RCTs with a combined total of 48 patients, cycling during HD for 30 minutes, 3x/week for 16 and 26 weeks led to a significant decrease in International Restless Leg Scale score as compared to no intradialytic exercise.^{15, 16} Similarly, a single RCT with 28 male participants showed significant improvement in Pittsburgh Sleep Quality Index score after 3 weeks of intradialytic cycling (5.85; SD 2.61) as compared with the control group (-1.00; SD -1.00).¹⁸ However, another study with 22 participants showed no significant difference between exercise and control groups in change in sleep quality measured by sleep diary after 26 weeks.¹⁵ Hadian et al. demonstrated that 83% of participants who exercised (walking for 20 minutes, thrice weekly for 8 weeks) had decreased cramping as compared with 31% of participants in the control group (p=0.014).¹⁹ Finally, using the Beck Depression Inventory and various exercise regimens (intradialytic cycling, walking or jogging outside of dialysis) for between 10 weeks to 1 year duration, several small RCTs have observed a 35-40% reduction in depressive symptomatology in exercisers as compared with non-exercise controls.²⁰⁻²⁴ The effect of exercise on mood has been more variable in studies that used other self-reported tools to measure symptoms of anxiety and depression.^{20, 23, 24, 25}

Although the signal provided by these small heterogeneous studies is promising, the impact of exercise on several common HD-related symptoms (nausea, extremity pain, dyspnea) is unknown and no study has examined the effects of exercise on overall symptom burden in HD. The opportunity to reduce symptom burden, address a knowledge gap important to patients and potentially improve functional status and HRQOL using an accessible, non-pharmacologic intervention underscores the importance of further research into the effects of exercise on symptom burden in ESKD.

2.1.3 Reduced symptom burden may be a major driver of improved HRQOL in ESKD

Not surprisingly, increased symptom burden is strongly associated with poor HRQOL and low functional status in individuals on HD. In 120 individuals within 3 months of commencing HD, greater symptom burden was associated with lower HRQOL as measured by the physical and mental components scores of the Short Form 36 (SF-36).⁹ Using the DSI, Weisbord et al demonstrated that the burden of mental and physical symptoms in HD patients were independently associated with poor HRQOL measured using the Illness Effects Questionnaire ($r=0.6$ and 0.61 , respectively).⁶ Finally, in a cohort of 301 Chinese HD patients with heavy symptom burden as measured by DSI, symptom burden was strongly correlated with reduced HRQOL as measured using the SF-36 ($r_s = -0.619$; $p < 0.001$).³³

Several recent systematic reviews of exercise programming in HD have demonstrated improvement in HRQOL as measured by generic self-reported instruments.^{14, 34} It is plausible that improved symptom control is a major driver of the improvement seen in HRQOL after exercise participation in this population. However, only a single study has investigated the effect of exercise on dialysis-related symptom burden using a questionnaire with limited previous validation and showed no benefit.²⁵ Using validated measurement tools for symptom burden and HRQOL with extensive previous use (DSI and EuroQol-5D3L respectively), we hope to further characterize the role of symptom burden in the improvements to HRQOL seen with exercise in the HD population.

2.1.4 Reduced symptom burden through exercise may decrease adverse outcomes

Dialysis confers an elevated risk of morbidity, which is further magnified in individuals with low physical function and physical activity levels.³⁵ Prospective observational studies in both incident and prevalent HD patients have found that individuals who are less active have a 30% higher mortality risk than individuals who are more active, even when adjusted for multiple confounders including age, sex, race, albumin, comorbidities, smoking and socioeconomic status.^{36, 37} This association was linear at all levels of activity, suggesting that even low functioning individuals on dialysis would benefit from becoming as active as possible.³⁷ Similarly, multiple observational studies have also shown that frail status and/or low self-reported physical function are associated with a 15-50% increase in falls, institutionalization and hospitalization rates among hemodialysis patients.³⁸⁻⁴³

Symptom burden also plays a role in the high rates of morbidity and mortality seen in the HD population.^{38, 44} In a large international observational study using DOPPS data that demonstrated a 25% increased risk of hospitalization and mortality with each 10 point decline in HRQOL, symptoms alone (measured by the Kidney Disease Component Summary), increased the risk of mortality and hospitalization by 8% when adjusted for albumin, comorbidities and other variables known to be associated with adverse outcomes.³⁹ In addition, restless legs, worsening insomnia and symptoms of depression have all been associated with a 30-40% increase in all-cause mortality risk in incident HD patients when adjusted for age, race, and comorbidities.^{17, 45, 46} Similarly,

depressive symptoms have also been associated with increased risk of hospitalization in incident HD patients.

Observational data suggest a link between low physical activity, low physical function, HD-related symptoms, poor HRQOL and increased hospitalization and mortality risks. No interventional trial has investigated the role of exercise programming on long-term outcomes. Our knowledge translation plan (Appendix 4) includes leveraging the methodology already in place for our study to gather the information required to design and implement a multicenter trial looking at the effect of exercise rehabilitation on long-term clinical outcomes, including frailty, hospitalization and mortality in HD.

2.2 Significance and rationale

Individuals on HD have high symptom burden, low functional status and poor HRQOL, for which effective treatments known to impact clinical outcomes are extremely limited. The identification of effective treatments for dialysis-related symptoms has been identified as a research priority by HD patients, their caregivers and healthcare providers in Canada.³⁰

In other chronic disease programs, exercise rehabilitation programs, incorporating resistance and aerobic exercise and lifestyle education, have demonstrated benefits to outcomes closely associated with symptom burden such as physical function, and HRQOL.^{47, 48} Although the immediate post-program benefits of such organized programs have been demonstrated for physical function and HRQOL outcomes in the ESKD population,^{21, 49, 50} *the effect of exercise rehabilitation on symptom burden in HD patients is unknown.*

We hypothesize that an exercise rehabilitation intervention will decrease symptom burden resulting in improved HRQOL and clinical outcomes such as functional status and frailty. Such results would have significant implications for individual Canadians with kidney disease, their caregivers and the healthcare system overall.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

The risks associated with study participation will be fully disclosed to participants. Occurrence of events will be monitored at every study visit, and will constitute grounds for termination of study intervention in study patients – these participants will remain in the study on a strictly observational basis.

Risk of Disclosure of Personal Health Information: There is a potential risk of disclosure of personal health information with any clinical study and database. All study personnel have undergone ethics, GCP CITI training, and taken a Pledge of Confidentiality (PHIA).

A secure study database will be maintained for the trial purposes. The study database will utilize appropriate security measures to protect patient privacy and data. All study participant information will be entered using a unique study identifier. All data and samples will be analyzed using the study identifier with no personal health information

linked to it. Each Site Principal Investigator will hold the key to the de-identified information in a locked and secure office. The Subject Identification Code List that links the identity of the participant with subject ID for de-identified data will be maintained with the trial's master file, according to ICH-GCP, Section 8.3.

Risk of Exercise: Participation in this trial of monitored exercise is low risk. Multiple previous studies of intradialytic exercise in individuals with ESKD have demonstrated no significant adverse events with such interventions. However, it should be noted that none of these studies were powered for safety outcomes. Participants will be carefully pre-screened for safety to exercise by the attending HD unit nephrologists and study staff and the program of exercise will be modified for each individual's personal health status and gradually incremental in intensity and duration. However, there is a certain degree of risk involved in the initiation of any exercise program. Patients will be monitored for the following risks:

- Muscle or joint soreness following initiation of an exercise program
- Low blood pressure on hemodialysis after exercising
- Develop chest pain (angina) during or after exercise
- Develop an irregular/fast heart rhythm (arrhythmia) during or after exercise
- Develop an acute coronary syndrome during or after exercise
- Develop hypoglycemia during or after exercise in setting of diabetes on medications
- Develop tendon rupture during or following exercise
- There is a very small risk of death related to the above side effects if they occur

2.3.2 Known Potential Benefits

The identification of effective treatments for dialysis-related symptoms has been identified as a research priority by HD patients, their caregivers and healthcare providers in Canada. In other chronic disease programs, exercise rehabilitation programs, incorporating resistance and aerobic exercise and lifestyle education, have demonstrated benefits to outcomes closely associated with symptom burden such as physical function, and HRQOL.^{47, 48} Although the immediate post-program benefits of such organized programs have been demonstrated for physical function and HRQOL outcomes in the ESKD population,^{21, 49, 50} the effect of exercise rehabilitation on symptom burden in HD patients is unknown.

Decreased symptom burden through exercise programming and the resulting improvements in HRQOL and clinical outcomes such as functional status and frailty would have significant implications for individual Canadians with kidney disease, their caregivers and the healthcare system overall.

3 OBJECTIVES AND PURPOSE

The **primary objective** of this study is to determine the effect of a 26-week exercise rehabilitation program consisting of structure lifestyle education, resistance exercise and intradialytic cycling on symptom burden at 12, 26 and 52 weeks in adult individuals on chronic hemodialysis.

Our **primary hypothesis** is that a participation in 26-week exercise rehabilitation program will decrease symptom burden immediately after the program at 12, 26 and 52 weeks in individuals on chronic hemodialysis.

Our **secondary objectives** include:

1. To determine the effect of a 26-week exercise rehabilitation program on health related quality of life at 12, 26, and 52 weeks.
2. To determine the effect of a 26-week exercise program on:
 - a. Time required for recovery post hemodialysis
 - b. Physical activity behavior at 12, 26, and 52 weeks
 - c. Exercise endurance/capacity at 12, 26 and 52 weeks
 - d. Frailty status at 12, 26, and 52 weeks
 - e. Self-efficacy to exercise at 12, 26, and 52 weeks
 - f. Hospitalization rate over 1 year and hospital length of stay
 - g. Mortality at 1 year

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This is a Phase 4 single-center prospective randomized controlled trial of prevalent adult chronic HD patients. Patients will be screened for eligibility **and one hundred and fifty patients** with dialysis-related symptoms as confirmed by baseline DSI symptom burden score > 0 will undergo 1:1 randomization to the two-step intervention (intensive and maintenance phase) and control arms for 1 year. The total study duration is approximately 4 years.

Please see the Schematic of the Study Design, p. 8.

4.1.1 Study Timeline

	Year 1				Year 2				Year 3				Year 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Patient Recruitment	■	■	■	■	■	■	■	■								
Ongoing Follow-up	■	■	■	■	■	■	■	■	■	■	■	■				
Statistical Analyses												■	■			
Knowledge Translation													■	■	■	■

4.2 Study Outcomes

4.2.1 Primary Outcomes

Change in symptom burden from baseline to 12, 26 and 52 weeks as measured by the Dialysis Symptom Index (DSI) Severity Score (Appendix B-1). This will be measured as the proportion of individuals who have a decline of 7 points or more in symptom burden as defined by DSI symptom severity score from baseline to 12 and 26 weeks. The DSI is a 30-item self-administered questionnaire with low administrative burden developed to measure the presence (yes/no) and severity (“how much did it bother you” by 5 point Likert-scale ranging from “not at all” to “very much”) of common emotional and physical symptoms over the previous week in individuals receiving maintenance HD.⁵¹ Symptom severity scores can range from 0 to 150. A 7-point change in severity score is likely to be clinically significant because this magnitude of change is: a) consistent with the resolution/addition of 1 “very bothersome” symptom plus a 1 point change in severity of 2 symptoms and likely to be significant to patients; and b) is approximately 1 standard error of the mean based on our pilot data (SD 30, n=18) and consistent with distribution-based methods. The DSI has been shown to be reliable in predicting HRQOL in multiple studies in North American and European HD populations.^{6, 51-53}

Change in symptom burden from baseline to 12, 26 and 52 weeks as measured by modified DSI Severity Score. Based on our experience and evidence from small clinical trials, we anticipate that the maximum benefit from exercise will occur in a subset of symptoms on the DSI. These include: a) muscle cramps; b) restless legs; c) feeling tired or lack of energy; d) difficulty concentrating; e) worrying; f) feeling nervous; g) trouble falling asleep; h) feeling irritable; i) feeling sad; j) feeling anxious. Thus, we will perform a subgroup analysis of DSI severity scores for the 11 symptoms listed above. This pragmatic approach will lead to less participant burn out than if individual measures were used for each symptom.

4.2.2 Principal Secondary Outcome

Change in generic HRQOL from baseline to 12, 26 and 52 weeks as assessed using the EuroQol (EQ) 5D-5L™ and EQ Visual Analogue Score (VAS) (Appendix B-2). This short self-administered generic tool consists of a descriptive system with 5 questions in 5-point Likert-type format, which assess how significantly the domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression are affected in daily life. The EQ-5D-5L Index, based on health state valuations elicited from the general public^{54, 55}, is anchored at 0.0 (dead) and 1.0 (full health). A minimum increment of 0.03 in the EQ-5D-DL index score can be considered clinically important as it corresponds to the smallest coefficient for a change from ‘No problem’ to ‘Some problems’ within a dimension of the EQ-5D-DL. The EQ VAS asks individuals to rate their current state of health from “worst imaginable” to “best imaginable” on a 100-point scale.⁵⁶ EQ-5D-5L™ is brief and has been extensively validated in various populations and disease states. Normative data for Canadians and ESKD exist.^{11, 57}

4.2.3 Secondary Outcomes

Participation in an exercise rehabilitation program may have additional benefits for patients that are not captured by the above outcomes. Therefore, the following secondary outcomes will be evaluated:

1. ***Change in time required for recovery following hemodialysis (in minutes) from baseline to 12, 26, and 52 weeks.*** At each study assessment, participants will be asked to answer the question “Approximately how much time does it take to recover from a dialysis session”. Answers will be recorded in minutes. Prolonged post-HD recovery time, defined as the answer to the question “How long does it take to recover from a dialysis session” has recently been identified as a troubling symptom complex and important outcome unique to individuals receiving HD.^{58, 59}

2. ***Change in physical activity behaviour patterns from baseline to 12, 26 and 52 weeks assessed:***

a. Using total active minutes per day as measured by multi-directional accelerometry. One week before each study assessment visit, participants will wear Actical Physical Activity Monitors™ (Philips Respironics, Bend, OR) on their dominant hip during waking hours for a period of 7 days with 15 second epochs. This technique is considered the gold standard for physical activity assessment.⁶⁰ During any cycling exercise, participants will wear the device on their dominant ankle. Valid files for analysis will require at least 3 days with a minimum of 8 h of wear time per day. Total active minutes will be calculated by summing the minutes per day spent in light intensity and moderate-to-vigorous physical activity (MVPA) based on pre-specified activity count cut points.^{61, 62} Accelerometry is included to adjust for physical activity in the control group and address potential contamination.

b. Using the Godin-Shephard Leisure-Time Exercise Questionnaire, which uses frequency and intensity of leisure time activity to calculate a total leisure time activity score.(REF) The total leisure time activity score has been validated against measures of physical fitness and objective measures of physical level activity collected by accelerometry in individuals with chronic disease.^{63, 64}

3. ***Change in Exercise Capacity from baseline to 12, 26 and 52 weeks as measured by Incremental Shuttle Walk Test (ISWT)*** (Appendix B-3). Total distance is recorded as individuals walk 10-meter lengths to self-reported exhaustion at pre-programmed progressively increasing speeds as indicated by recorded beeps. ISWT has been used repeatedly in elderly and CKD populations, minimal clinically important differences have been established in chronic disease populations and results are correlated with other measures of exercise capacity.^{65,66-68} ISWT was chosen to objectively measure physical function because standardized walking speeds at each stage make it less subject to measurement error due to variable participant effort than other similar tests.

4. ***Change in frailty status from baseline to 12, 26 and 52 weeks assessed using the Modified Fried Criteria.***^{69, 70} Defined as the presence of ≥ 3 criteria of the following criteria: weight loss; exhaustion; slowness; low physical activity; and weakness. As a

predictor of adverse outcomes and associated with symptom burden, it is important to determine if frailty status can be modified through exercise

5. Change in self-efficacy for exercise from baseline to 12, 26 and 52 weeks assessed using the Self-Efficacy for Exercise Survey (Appendix B-4). This self-reported tool consists of 9 brief questions in 10-point Likert scale format.⁷¹ The summary score indicates an individual's perception of their ability to successfully incorporate physical activity into daily routine and is the strongest determinant of continued exercise participation following formal exercise or rehabilitation programs.⁷² This measure has reliably predicted physical activity behavior in elderly individuals from various cultural backgrounds.^{71, 73, 74}

6. Hospitalization rate defined as the number of hospitalization days admitted per patient year. In addition, cause and length of any hospital stay for greater than 24 hours will be collected. At each study assessment time point, this will be determined by self-report and hemodialysis chart review.

7. All-cause mortality defined as the proportion of patients who die over 1-year and cause of death obtained from dialysis unit records. Depending on number of events, analysis may be adjusted for time on dialysis, age and comorbidities.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Participant Enrolment Inclusion Criteria

This pragmatic clinical trial is designed to evaluate a “real-world” setting, requiring a broad study population. In order to be eligible, study participants must meet the following criteria:

1. Adults (> 18 years old) who are > 3 months after starting chronic HD;
2. No expected change in dialysis modality or relocation outside of Winnipeg during the intervention period (26 weeks);
3. Assessed to be safe and able to exercise by the HD unit nephrologist¹;
4. Able to understand and provide written informed consent

5.2 Participant Enrolment Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from participation:

1. Acute coronary syndrome in the past 3 months;
2. Unstable arrhythmia;
3. Shortness of breath at rest or with minimal activity (NYHA Class 4);
4. Symptomatic hypoglycemia (>2x/week in week prior to enrolment);
5. Currently participating in the Manitoba Renal Program’s clinical intradialytic cycling program;
6. Score of ‘0’ on Dialysis Symptom Index when administered at time of consent;

5.3 Strategies for Recruitment and Retention

A total of **150** chronic adult hemodialysis patients will be randomized at the 4 Winnipeg HD units over 2 years or until the target enrolment has been achieved. Approximately 325 individuals commence chronic HD in Winnipeg per year. At any time, there are approximately 700 prevalent patients receiving in-centre HD in Winnipeg. Assuming eligibility rate of 40% and a conservative 25% enrolment rate (based on previous studies and pilot data), the targeted sample size is achievable over the proposed 2-year study period and would amount to a maximum of 5 patients cycling per shift at each of the 4 HD units involved in the study at any one time. Based on our clinical cycling program experience (where we have up to 10 individuals cycling per shift), this rate of enrolment is easily achievable.

¹ Nephrologists will be provided with verbal instructions and written guidelines to loosely follow when assessing for safety to exercise

Recruitment feasibility: We anticipate meeting the target enrolment within the study period given: a) the size of the target in-centre hemodialysis population outlined above and; b) we have selected a minimal number of clinically relevant inclusion criteria based on input from clinicians and clinical trialists (Canadian Nephrology Trials Network, CNTN)⁷⁵ to maximize study eligibility and participant generalizability.

Recruitment organization: Posters and study information brochures may be used to facilitate recruitment. All recruitment materials will have been reviewed and approved by the REB prior to use.

Recruitment management: Enrollment progress will be evaluated monthly, and in the event that enrollment targets are not met per the recruitment schedule, the recruitment of an additional study site (Calgary: co-PI J. MacRae) will be considered.

Recruitment retention: Participants will be reimbursed for travel to study appointments at a rate of \$20 per round trip for each study appointment attended.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

Participants will complete the study after their 12-month study visit is complete. Participants are free to withdraw from participation in the study at any time, for any reason, specified or unspecified without penalty. Participants may also be withdrawn from the study if, in the opinion of the Investigator, it is in their best interests to do so. Participants may also be withdrawn from the study for any of the following reasons:

1. The participant is “lost to follow-up” (i.e. no further follow-up is possible because attempts to re-establish contact with the subject have failed);
2. The participant meets an exclusion criteria, either newly developed or not previously recognized, that precludes further study participation;
3. Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant;
4. Death.

5.4.2 Handling of Participant Withdrawals or Termination

Participants who withdraw will not be replaced in the event that the target accrual rate for randomization is obtained. If the overall target accrual rate is lower than expected, or the drop-out rate is higher than expected, then recruitment will continue to reach the target study number.

If there is a reason for medical withdrawal, the participant will remain under the care of their primary dialysis nephrologist. The primary investigator will be available for

consultation as needed. The date and reason for withdrawal will be documented in the participant's record. If a participant is prematurely terminated from the study for any reason, they will be asked to complete a final study exit visit and/or final outcome assessments. Every effort will be made to obtain final data collection on treatments and outcomes, to reduce potential sources of bias. Follow-up for unresolved adverse events reported at the time of withdrawal will be the same as outlined in the adverse event section of the protocol.

5.4.3 Participant Suspension from the Study

The site principal investigator may temporarily suspend the study protocol if they judge that the participant's health would be temporarily at risk in continuing the study protocol, such as with the occurrence of an acute illness requiring hospitalization;

Participants should not re-commence the study protocol, until BOTH the attending dialysis nephrologist and the site principal investigator feel that the medical condition has resolved and the participant is safe to resume the protocol.

5.5 Premature Termination or Suspension of the Study

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. The study PI and the Data Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. Notification of, including written documentation of the reason for study suspension or termination will be provided by the suspending or terminating party to the PI, REB, and regulatory authorities as applicable. Circumstances that may warrant termination of the study or suspension include:

1. Determination of unexpected, significant, or unacceptable risk to participants, such as:
 - Severe adverse events related to the exercise intervention, rates above expected (>20% of participants develop new angina, new arrhythmia, myocardial infarction, serious hemodialysis access complications or tendon rupture);
2. Across both Intervention and Control Arms, incidence of:
 - Death rates above expected, and attributable to the study protocol.
3. Insufficient compliance to protocol requirements.
4. Data that is not sufficiently complete and/or evaluable.

5.5.1 Independent Data Safety Monitoring Board (DSMB)

The DSMB will be composed of 2 third party researchers and a statistician/analyst (Drs. Quinn and Ravani – University of Calgary, AB; R. Brar, University of Manitoba). Safety data will be reviewed at least yearly at planned DSMB Data Review Meetings. Serious adverse events (see below) will be reported and reviewed immediately by the DSMB Chair. The

DSMB will provide recommendations for continuation or early termination of the trial based on assessment of safety. The DSMB may also make recommendations related to the selection, recruitment or retention of participants, their management and adherence to protocol-specific regimens, and the procedures for data management and quality control.

5.5.2 Ascertainment and Documentation of Adverse Events for DSMB:

1. At each study assessment visit, study participants will be asked by the independent outcome assessor at clinic if they have experienced any of the adverse (AE) or serious adverse events (SAE) on the list below.
2. In addition, the research coordinator will identify any AEs or SAEs through review of participants' hemodialysis charts at each assessment time point.
3. Study kinesiologist and research coordinator will also track events if noted during their interaction with patients.
4. Study staff will communicate with dialysis staff to inform them regarding the types of issues that constitute AEs and SAEs. Dialysis staff will be asked to report any such occurrences to study staff as soon as possible.

5.5.3 List of Adverse Events to Be Collected for DSMB

Adverse Events:

1. Fistula blow
2. Muscle aches or pains
3. Symptomatic Intradialytic hypotension (BP < 90 mmHg or 20 mmHg drop from baseline associated with symptoms such as headache, cramping, dizziness, nausea)
4. Intradialytic cramping
5. Increasing fatigue
6. Symptomatic hypoglycemia (sugar < 4 associated with typical symptoms of hypoglycemia)
7. Fall
8. Foot ulcer

Serious Adverse Events:

1. Chest pain while exercising (either intradialytic or outside of dialysis)
2. Arrhythmia while exercising (either intradialytic or outside of dialysis)
3. Unstable hemodialysis necessitating transfer to emergency post hemodialysis
4. Tendon rupture
5. Fall with fracture
6. Admission to hospital for any cause
7. Acute coronary syndrome
8. Death from any cause

6 STUDY AGENT

6.1 Study Agent(s) and Control Description

This study does not involve an investigational drug and is therefore, CTA exempt.

7 STUDY SPECIFIC PROCEDURES

7.1 Study Procedures/Evaluations

The study-specific procedures and time-points to be done over the course of the study are summarized below and in Section 7.3 of the protocol:

Enrolled Study Population (both study groups)

- Informed Consent (enrolment, visit 0)
- Final study eligibility assessment including administration of DSI (enrolment, visit 0)
- Randomization (baseline)
- Collect Baseline Demographics – age; gender; ethnicity/race (baseline, visit 1)
- Collect Past Medical History – cause of end stage renal disease; diabetes; hypertension; smoking; cardiac disease/arrhythmia; cerebrovascular disease/stroke/transient ischemic attack; lung disease; peripheral vascular disease/lower extremity amputation; arthritis; date of dialysis start; other relevant medical history (baseline, visit 1)
- Collect Concomitant Medications (each study visit)
- Collect vital signs/clinical data - height, weight, BMI, systolic and diastolic blood pressure; dialysis adequacy (Kt/V); weekly intradialytic fluid gains; duration of HD and heart rate (each study visit; height will only be done on the 1st baseline visit)
- Collect Clinical Laboratory results (each study visit):
 - Blood: hemoglobin, calcium, albumin, phosphate
- Patient compliance with the study protocol will be monitored in accordance to the Monitoring Plan (each study visit)
- Dialysis Symptom Index (enrolment visit and each study visit)
- EQ-5D-5L (each study visit)
- Time required for recovery following hemodialysis (each study visit)
- Download 7 day accelerometry history (each study visit)
- Godin-Shephard Leisure-Time Exercise Questionnaire (each study visit)
- Incremental Shuttle Walk Test (each study visit)
- Frailty status using the Modified Fried Criteria (each study visit)
- Self-Efficacy for Exercise Survey (each study visit)
- Cause and length of any hospitalization since last study visit (study visit 2, 3 and 4)
- Death (study visit 2, 3 and 4)

- Physical activity/exercise logs (collected weekly for first 12 weeks then every 2 weeks for next 40 weeks)

Intervention Group – Additional Evaluation

- Maximal incremental cycle test to volitional exhaustion⁷⁸ (After randomized to intervention and before intervention started)

7.1.1 Demographic Data Collection

The research assistant will collect demographic data at the baseline assessment visit via patient interview and hemodialysis chart review. Data collected will include age, gender, race, cause of renal failure, dialysis vintage (time on hemodialysis), comorbidities (cardiovascular disease, congestive heart failure, diabetes mellitus, arthritis, peripheral vascular disease, cerebrovascular disease, malignancy, lung disease), use of walking aid (type), smoking history.

7.1.2 Clinical Data Collection

The research assistant will collect clinical data at baseline, 12, 26, and 52-week assessment visits via hemodialysis chart review. Data collected will include the following:

1. **Medications:** (eprex weekly dose, blood pressure medications and dosage, cardiac medications). The research assistant will photocopy the most recent de-identified Renal Medication Flow sheet in the hemodialysis chart to include in the research chart.
2. **Dialysis Clearance:** mean Kt/V for the 3 HD sessions immediately preceding the study assessment
3. **Blood pressure:** Systolic and diastolic blood pressure pre and post hemodialysis at the hemodialysis session immediately preceding the study assessment
4. **Heart Rate:** Heart rate (sitting) pre and post hemodialysis at the hemodialysis session immediately preceding the study assessment
5. **Duration and frequency** of hemodialysis sessions
6. **Dialysis prescription:** Dialysis time, frequency of HD sessions, Dialysate potassium, sodium and calcium, dry weight
7. **Mean fluid gains:** the total volume (L) of fluid gained between interdialytic sessions during the week (3 HD sessions) prior to the study assessment

7.1.3 Laboratory Data Collection

The research assistant will collect laboratory data 12, 26, and 52-week assessment visits via hemodialysis chart review. The monthly blood work results taken at the closest time point to the study visit will be transcribed to CRF forms from HD chart at each study assessment time point. Monthly blood work samples are taken pre-dialysis on a mid week dialysis day routinely as standard of care in in-centre hemodialysis. Hardcopy print out of results is placed in the hemodialysis chart as routine standard of care. Lab results collected

will include: Hemoglobin, albumin, potassium, calcium, phosphate, parathyroid hormone. No additional blood samples will be required for this study.

7.2 Study Outcome Evaluations

Outcome assessments (as detailed in Section 4.2) will occur at baseline, 12, 26 and 52 weeks (within +/-10 days of this time point) and be performed pre-dialysis on a midweek dialysis day to minimize the effects of fluid overload and dialysis fatigue, but maximize convenience and adherence to the assessment schedule. In our pilot study, assessment visits took 30 minutes.

7.3 Study Schedule

A detailed description of each study procedure is available in Section 7.1:

Scheduled Study Procedure	Screening/ Enrolment (Visit 0)	Baseline (Visit 1)	Mid Intervention 12 weeks (Visit 2)	End Intervention 26 weeks (Visit 3)	Final Visit 52 weeks (Visit 4)
Informed Consent	X				
Final Study Eligibility	X	X			
Demographics		X			
Medical History		X			
Physical/Clinical Assessment		X	X	X	X
Concomitant Medications		X	X	X	X
Safety Monitoring Adverse Events		X	X	X	X
Protocol Compliance		X	X	X	X
Dialysis Symptom Index	X	X	X	X	X
EQ5D-5L/EQVAS		X	X	X	X
Time to recover from HD		X	X	X	X
Accelerometry		X	X	X	X
Godin-Shephard Leisure Time Exercise Questionnaire		X	X	X	X
Incremental Shuttle Walk Test		X	X	X	X
Frailty Status		X	X	X	X
Self-Efficacy for Exercise Study		X	X	X	X
Hospitalization history			X	X	X
Death			X	X	X
Collection of exercise logs			WEEKLY	EVERY 2 WEEKS	
Incremental Cycle Test	(X)*				

*In intervention group only between enrolment visit and start of intervention

7.3.1 Screening Phase, Consent, Enrolment

All prevalent adult renal transplant patients who can provide informed consent will be considered for enrolment and this will be done at the HD units (Sherbrook Centre Dialysis; Health Sciences Centre Central Dialysis Unit., St. Boniface General Hospital Dialysis Unit and Seven Oaks General Hospital Dialysis Unit).

A patient's verbal assent to meet with the research nurse/coordinator will be obtained by the clinical team. The patient will be contacted by the research nurse/coordinator, the study will be briefly described and the applicable inclusion/exclusion criteria will be reviewed with the patient by the research nurse/coordinator to cursorily assess their study eligibility. Patients who meet the exclusion criteria after this cursory review will be thanked for their time and will not proceed further. If a patient appears to meet the applicable inclusion/exclusion criteria after this cursory eligibility review and is interested in proceeding, the study consent form will be provided and reviewed in lay terms with this patient. A unique participant identifier will be assigned to each patient consented and enrolled for the study. A screening log will be maintained at each site to record all individuals screened for participation in the study. All participants will provide their written informed consent form before undergoing any study procedures.

Once informed consent is obtained, the DSI will be administered to all participants. If patients score '0' on the DSI (no symptoms), they will be deemed ineligible for the study and will not proceed further. Pilot data suggests 40% of in-centre HD patients will be eligible; the majority of ineligibility in our pilot study was due to modality or hospital change.

Once final eligibility is confirmed, baseline assessment at the individual's HD unit will be arranged, at which all participants will receive standardized counseling regarding the benefits of physical activity (usual care)⁷⁶ and undergo baseline testing for study outcomes. This appointment will also serve as a "run-in phase". Those that fail to attend will not be enrolled.

7.3.2 Randomization and Blinding

Participants will be randomly assigned to the Intervention Arm or Control Arm. Randomization will be performed by a third party using *block randomization* with randomly permuted block sizes with an overall 1:1 allocation. To ensure *allocation concealment* and to *minimize bias*, the randomization code will not be released until baseline testing is completed. After randomization has occurred, the site's research staff will be responsible for ensuring the assigned randomization number is applied to all study documents for each participant. Due to the nature of the intervention in this trial, randomization to the Intervention Arm cannot be blinded to the site PI's or participants. However outcome assessors and study statistician will be blinded to study group during analysis (Prospective Randomized Open Blinded-Endpoint study).

7.4 Study Groups

7.4.1 Control Arm, Standard-of-care

As recommended in clinical practice guidelines for individuals with CKD, participants will receive standardized exercise counseling at baseline.^{76, 77} Although not prohibited from participating in exercise outside of the study protocol, participants in the control group will not undergo a formal structured exercise intervention and will be asked to refrain from intradialytic cycling during the 26-week intervention period. Exercise activity will be tracked via weekly self-reported log sheets. The study kinesiologist (to control for personal trainer effect) will collect log sheets weekly during the study period. Outcome measurements will occur according to the Schedule of Events (**Section 7.5**).

7.4.2 Intervention Arm, Exercise Rehabilitation Program

Participants will receive exercise counseling as per controls. To standardize intervention exercise intensity, a maximal incremental cycle test (to volitional exhaustion)⁷⁸ will be performed prior to hemodialysis on a mid-week dialysis day on an ergometer in the hemodialysis unit or at the Wellness Institute depending on availability of testing equipment and patient preference. Participants will then participate in a 26-week exercise rehabilitation program as follows (See Section 7.4.5 Study Intervention Schematic):

1. Standardized one-on-one lifestyle education sessions at HD provided by the study kinesiologist: Self-management exercise education using Wellness Institute Cardiac Rehabilitation program modules for 1 hr/wk during the first 4 weeks of the intervention. An additional 4 standardized sessions focused on maintenance of lifelong physical activity will be provided over the remaining intervention period.

2. Resistance training, using tubing and body weight, based on established guidelines:^{79, 80} Weekly resistance training education will be provided by the study kinesiologist in one-on-one format at HD during the first 4 weeks of intervention. Resistance training bands, instructions and logbooks provided for home exercise (goal 2 sessions/week) during the 26-week intervention period (See Section 7.4.6 Summary Exercise Rehabilitation Program).

3. Intradialytic cycling during HD (intensive and maintenance phase): Participants will cycle on TherapyCycle™ (Greely, CO) ergometers modified for dialysis beds or chairs⁸¹ with an initial target exercise intensity of 50-60% of individual maximal workload as determined by the incremental cycling test.^{49, 82} Target exercise duration will be 60 minutes in the first half of each HD session, 3 times per week for 26 weeks. Rest periods will be provided as needed if participants are unable to complete 60 minutes of continuous exercise.^{82, 83} Duration of total exercise time, average workload (Watts) and self-reported exercise intensity as measured by Borg Rating of Perceived Exertion (RPE) will be recorded by participants for each exercise session. Target Borg RPE will be 13, which is considered to

be moderate intensity.⁸⁴ Ergometer resistance will be adjusted over time by the study kinesiologist as triggered by a 1-point change in Borg RPE.

During the initial 3 intradialytic exercise sessions, the study kinesiologist will supervise participants closely. Following 3 sessions (or more if required), HD unit staff will assist with set up of the cycle ergometers and monitoring during exercise sessions.

During the *intensive phase* (first 13 weeks) of the intervention, the study kinesiologist will check in on a weekly basis (at a minimum) with participants and staff to address problems and questions as needed. Subsequently, during the *maintenance phase* of the intervention (latter 13 weeks), the kinesiologist will check in every two weeks to help with intensity adjustment, encouragement, motivation and troubleshooting. All exercise activity performed outside of HD, including resistance training will be tracked weekly by self-report using home log sheets during the intervention phase and then bimonthly until study end (see Section 7.4.5 Study Intervention Design Schematic).

7.4.3 Exercise following the intervention period

If offered as a clinical program in their HD unit, participants will be able to participate in intradialytic cycling *after the intervention phase*, regardless of study group.

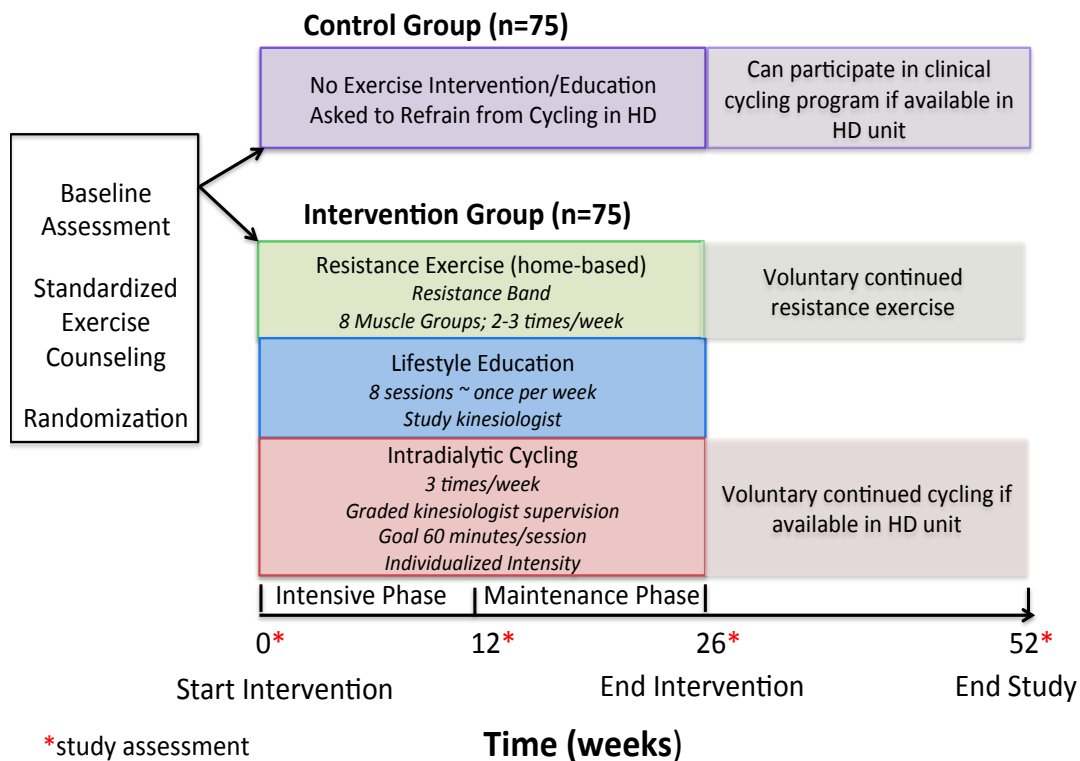
7.4.4 Adherence to the exercise intervention

Adherence to will be assessed in the intervention group by:

- (a) Proportion of resistance and intradialytic cycling exercise sessions logged compared to total number of possible exercise sessions
- (b) Proportion of total minutes of intradialytic cycling achieved based on logbook records compared to goal intradialytic cycling minutes.

7.4.5 Study Intervention Design Schematic

Figure 1: Study Design Schematic



7.4.6 Summary of Exercise Rehabilitation Program

Type of Intervention	Frequency	Time	Duration	Intensity	Location
One-on-One Exercise Education	1x/wk	1 hour	8 weeks	Not applicable	HD Unit
Resistance Exercise	2x/wk	8 muscle groups^ Goal: 12-15 reps/muscle	26 weeks	8 repetition max Goal RPE*= 12-13	Home
Cycling during HD	3x/wk	Goal: 60 minutes	26 weeks	50-60% max workload (Cycling test) Goal RPE=13	HD Unit

^ biceps, triceps, chest muscles, hamstrings, quadriceps, hip extensors and hip abductors

7.5 Concomitant Medications, Treatments, And Procedures

All medication prescription and changes, dialysis treatment prescription and changes and other medical care will be the responsibility of the attending dialysis unit nephrologist and other usual physicians. Changes in the above parameters will be recorded by research staff during scheduled study visits.

7.6 Prohibited Medications, Treatments, And Procedures

Participants in the control arm will be asked to refrain from intradialytic cycling during the 26-week “intervention” period. No medications, treatments or procedures will be otherwise prohibited as part of the study.

7.7 Exercise Records

All exercise performed by participants in the control and intervention group will be recorded by participants on a weekly basis in self-reported log sheets.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

All adverse events (AEs) and serious adverse events (SAEs) will be classified by body system and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs will be summarized as the frequency of each event in the treatment group.

Frequency tables by treatment group and category of event (e.g., serious, related to study therapy, causing the discontinuation of study intervention) and by National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity grade will be presented. Selected laboratory values will also be summarized in the treatment group using the mean and standard deviation of the change from baseline at scheduled visits.

8.1.1 Definition of Adverse Events (AEs)

An adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease that occurs during participation in the trial.

8.1.2 Definition of Serious Adverse Events (SAEs)

An SAE or reaction is any untoward medical occurrence that at any dose leads to any of the following events:

1. Death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up must be reported whether it is considered to be treatment related or not.
2. A life-threatening event. A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the patient or subject at immediate risk of death from the reaction as it occurred.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability.
5. An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
6. Congenital anomaly or birth defect.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

The study site will grade the severity of adverse events experienced by study subjects according to the NCI-CTCAE Version 4.0 (published May 28, 2009). This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs. Adverse event general grade definitions are summarized as follows:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization or hospice care probable.
Grade 5	Death	Death.

Adverse events, not included in the NCI-CTCAE, will be recorded and graded 1 to 5 according to the General Grade Definition provided above.

8.2.2 Relationship of an Adverse Event

The relationship, or attribution, of an adverse event in the study will initially be determined by the principal investigator. The PI will also record the determination of attribution on the appropriate CRF and/or SAE report form. The relationship of an adverse event will be defined by using the descriptors provided in the table below.

Code	Descriptor	Definition
UNRELATED CATEGORY		
1	Unrelated	The adverse event is definitely not related to the study therapy regimen.

RELATED CATEGORIES		
2	Possible	The adverse event might or might not be related to the study therapy regimen (This grade is assigned when uncertainty exists)
3	Definite	The adverse event is definitely related to the study therapy regimen

8.2.3 Expectedness

All AEs (grade 2 or higher) that occur after enrollment will be reported.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

Adverse events will be collected from the time the participant completes the first protocol mandated procedure until the subject has completed the study. Adverse events may be discovered through any of these methods:

- Observing the subject.
- Questioning the subject, this should be done in an objective manner.
- Receiving an unsolicited complaint from the subject.
- An abnormal value or result from a clinical or laboratory evaluation.
- Report from HD unit nephrologists or nurses

In association with the attending dialysis unit nephrologist, the PI will provide appropriate medical care to participants experiencing AEs until their symptoms resolve, their status stabilizes, or until 30 days after a participant terminates from the study, whichever comes first.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

The PI is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE). All AEs will be recorded in the source documents and on the appropriate CRF(s). All data will be reviewed twice yearly by the DSMB, which may provide recommendations to the study PI about withdrawing any participant and/or terminating the study because of safety concerns.

8.4.2 Serious Adverse Event Reporting

The PI is responsible for the detection and documentation of events meeting the criteria and definition of a serious adverse event (SAE). Serious adverse events will be collected from the time of the randomization until the study completion, or until 30 days after the subject prematurely withdraws from the study.

After learning that a participant has experienced an SAE, the PI is responsible for reporting the SAE as per REB's guidelines. The SAE report will be completed within 7 working days of the reported event. The DSMB may request to receive real-time notification of all SAEs thought to be related to the treatment procedure. At the time of the event, as much information as possible must be collected, but at a minimum must include the following:

- AE description
- Relationship to study exercise intervention.
- Relationship to protocol mandated procedures
- Reason why the event is serious.
- Supplementary CRF pages that are current at the time of SAE reporting: medical history, concomitant medications, demographics, death.

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. As additional details become available, the SAE CRF should be updated and submitted to the site's ethics committee.

8.5 Safety Oversight

Safety oversight will be under the direction of an independent DSMB. The DSMB will meet at least annually to assess safety and efficacy data on each Arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The study PI will provide the DSMB with listings of all SAEs on an ongoing basis. The DSMB may request to receive real-time notification of all SAEs thought to be related to the treatment procedure.

The principal investigator will ensure the timely dissemination of SAE information to the Ethics committee in accordance with applicable guidelines.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical and Analytic Plan

An outline of the analytic methods are given below.

9.2 Sample Size and Power

Based on the limited literature published in this area, we expect an absolute difference of 25% between the intervention and control groups in the proportion of individuals in whom DSI severity score decreases by 7 points or more over time.

We predict DSI score will decrease in 50% of the intervention group and 25% of the control group at 12 weeks (baseline prevalence of symptoms assumed to be 50%). A sample size of 58 patients in each arm will allow us to detect this difference with 80% power (alpha 0.05). We conservatively anticipate 30% dropout.⁸³ Therefore, a target sample size of 150 participants (75 participants per study arm) is proposed.

This sample size will allow us to detect a 7-point difference in mean change in DSI severity score using standard deviation of 16 with 80% power and alpha 0.05. This sample size (n=75 in each arm) will also provide 80% power with 0.05 alpha to detect a 12-point difference between groups in mean change in HRQOL measured using EQ-VAS (considered clinically important difference in other chronic diseases)⁸⁵ and a 30% absolute difference in proportion of individuals endorsing deficits in each domain of EQ5D-3L over time assuming 50% baseline deficit and development of new deficits in an additional 10% of the control group and a reduction in deficits in 15% of the intervention group.

9.3 Feasibility

Approximately 325 individuals commence chronic HD in Winnipeg per year. At any time, there are approximately 700 prevalent patients receiving in-centre HD in Winnipeg. Assuming eligibility rate of 40% and a conservative 25% enrolment rate (based on previous studies and pilot data), the targeted sample size is achievable over the proposed 2-year recruitment period (see Section 4.1.1) and would amount to a maximum of 5 patients cycling per shift at each of the 4 HD units involved in the study at any one time. Based on our clinical cycling program experience (where we have up to 10 individuals cycling per shift), this rate of enrolment is easily achievable.

9.3 Description of Statistical Methods

9.3.1 Primary Outcome

Developed in consultation with a statistician (T. Ferguson, Chronic Disease Innovation

Centre) familiar with RCTs and our study outcomes, analysis will be performed in an intention-to-treat manner on a case available basis. Change in DSI severity score over time will be compared between groups by independent two-tailed t-test or Mann-Whitney U test depending on distribution and using generalized linear mixed models. Proportion of individuals whose DSI severity score has changed by 7 or more points will be compared between groups at each study time point using Chi-square test.

Multiple logistic regression will be performed to determine predictors of change in DSI severity score over time and adjusted for time varying confounders using a marginal structural model. Although study group will be the primary predictor in this model, other key predictors of symptom burden (including diabetes status, ischemic heart disease (IHD), age, gender, race, smoking status, serum albumin level, hemoglobin, baseline physical function, physical activity level) will also be tested in a step-wise manner.

If **missing outcome data** is greater than anticipated (25%) we will impute them according to current FDA/NAS/NRC recommendations using multiple imputation with chained equations⁸⁶⁻⁸⁸. Specifically, multiple imputation creates 20-40 complete datasets with plausible values from the model-based predictive distributions, and pooled estimates and standard errors are obtained through the use of Rubin's combining rules. These models are predicated on the assumption that the data are missing at random (MAR). Finally, the robustness of the inferences about treatment effects to violations of the MAR assumptions will be evaluated through a sensitivity analysis⁸⁸.

9.3.2 Planned Sub-group Analyses

Sub-group analyses may require adjustment for prognostic imbalances, as the effect of randomization may not be preserved.

Gender analysis: A sub-group analysis is planned by gender as effect of exercise may vary by gender.

Physical activity level: A subgroup analysis is planned by quartiles of baseline physical activity level as measured by accelerometry at baseline. Level of baseline physical activity may modify the effect of the intervention and is an important potential confounder.

On protocol analysis: Non-adherence to the exercise intervention may modify the effect of the intervention and is an important potential confounder. Therefore, a pre-specified analysis of the primary outcome will be performed "on protocol", defined by adherence to intervention protocol as defined by completion of 80% or greater of exercise sessions during the intervention period.

9.3.3 Secondary Outcomes and Analyses

Change in EQVAS over time will be compared between study groups using Student's T-test. As well, we will compare the difference in proportion of individuals who develop new deficits (score of 2 or 3) in each domain of the EQ5D-5L over time. The degree to which change in symptom burden correlates with change in EQVAS will be assessed using Spearman and Pearson's correlation coefficients as indicated based on distribution of the data. Change in all other secondary outcomes over time will be compared between groups using the appropriate parametric and non-parametric statistical tests depending on data type and distribution. Hospitalization will be analyzed using Poisson regression. For all analyses, two-sided $p < 0.01$ will be statistically significant. Statistical analysis will be performed using SAS 9.3 (Carey, NC).

We will validate the Godin Shepard Leisure-Time Exercise Questionnaire using accelerometry data. Correlation between Godin Questionnaire Score and active minutes (light, moderate and moderate-vigorous activity) measured by accelerometry at each study assessment time point will be assessed using Pearson or Spearman correlation depending on distribution of the data. Internal consistency of the Godin questionnaire will be assessed using Cronbach alpha and Intraclass Correlation Coefficient. In those individuals in which active minutes measured using accelerometry did not change between assessment periods (change of less than 10% from baseline), test re-test reliability of the Godin Questionnaire will be assessed using Kappa statistic. Responsiveness will be modelled using linear regression with Godin questionnaire score as the primary predictor of active minutes measured by accelerometry. Additional predictors including sex, age, diabetes and other comorbidities will be added to the model as sample size will allow.

9.3.4 Demographic Data

Statistical presentation for baseline and demographic characteristics will be reported. Specifically, we will compare baseline descriptive variables between study groups using independent two-tailed t-test or Mann Whitney U test for continuous variables and Chi-square test for categorical variables, as appropriate. Similarly, individuals who complete the study protocol will be compared to those who do not. As per the latest FDA/NRC/NAS guidelines for the treatment of missing data in clinical trials, the same data will be tabulated for patients with incomplete records. If missing outcomes are greater than 25%, multiple imputation techniques will be used as per FDA recommendations.⁸⁸

9.3.5 Study Completion

The percent of participants who complete the study, losses to follow-up, times to lost to follow-up, and reasons for discontinuation (e.g., adverse events) will be presented.

9.3.6 Final Study Analysis

The final study analysis will report the results of the above statistical analysis plan. Any additional analyses will be identified as ad hoc. A final clinical studies paper(s) will be prepared.

10 STUDY ADMINISTRATION AND ETHICAL CONSIDERATIONS

10.1 Source documents and Access to Source Data/Documents

The study site will maintain appropriate medical and research records for this study, in compliance with ICH-GCP, and institutional requirements.

In this study, CRFs will be the primary record of the patients' participation in the study, but will be supplemented by hard copy documentation of outcome assessments (e.g. completed surveys).

10.2 Ethics Approval

Submission of this protocol and the required participant-related documents (consent form, advertisements) will be made to site's REBs and/or for institutional review (if required). Written approval from the REB will be obtained in writing prior to implementation. Any changes made to the protocol and participant-related documents will be submitted for review and approval prior to implementation. Study status will be reported annually or more frequently if required. A final study notification will be forwarded at completion of the study or in the event of early termination. All serious adverse events and protocol deviations (if applicable) will be submitted for review.

10.2.1 Protocol Deviation Definitions

Protocol Deviation: The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly. Protocol deviations may be major or non-major.

Major Protocol Deviation (Protocol Violation): A protocol violation is a deviation from the ethics-approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations.

Non-Major Protocol Deviation: A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

10.2.2 Reporting and Managing Protocol Deviations

As per ICH GCP, the Investigator should not implement any deviation from, or changes of the protocol without prior review and documented approval/favorable opinion of the ethics committee or institutional review board of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only

logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)). All protocol deviations (both minor and major) that have not received prior approval by the ethics committee must be reported to the ethics committee as per their applicable reporting requirements. The study coordinator will report all protocol deviations to the study PI. Where safety is involved, the DSMB will also be notified.

10.3 Informed Consent Process

Voluntary written informed consent will be obtained from all participants. A member of the site's research team (study coordinator or research nurse) will review the consent with the participant and answer questions. Participants will be given both verbal and written information that provides a detailed description of the study. Participants will be provided adequate time to consider the risks and benefits associated with their participation in the study (at least 48 hours). They will be told that participation in the study is voluntary and that he or she may withdraw from the study at any time without penalty, and the decision will not impact their standard medical care.

The procedures for conducting informed consent will be documented in the participant's study record. All participants will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be available in English and the information will be provided with assistance of a translator as requested. A copy of the signed consent will be given to the participant. All original signed consents will be filed in the study binder and maintained in PI's office.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

10.4 Participant and Data Confidentiality

All members of the research team will respect study participants' privacy and confidentiality throughout the study. Measures will be taken to ensure that all of the data collected for this study will remain confidential in accordance with privacy legislation. Study personnel will not transmit documents, other than that previously specified, or samples containing personal health identifiers (PHI) at any time over the course of the study. Each participant will be assigned a unique code and these numbers rather than names will be used to collect, store, and report participant information. Full names and other identifying information will not be revealed unless required by law and/or for the applicable REB review, or for auditing purposes. The Subject Identification Code List that links the identity of the participant with subject ID for de-identified data will be maintained with the trial master file, according to ICH-GCP, Section 8.3. The master file will be maintained both in electronic and paper copy format. The electronic file will be encrypted and stored on a dedicated research server that only the PI and study research staff will have access to. The identity of the participants will not be revealed in any

published data or in presentation of the information obtained as a result of this study. Findings will be reported in aggregate.

10.5 Data Collection and Management

Data will be submitted for every participant who is enrolled in the study, regardless of duration via paper Case Report Form or through a secured electronic data capture system (i.e. REDCap). Data available from the source documents will be either transcribed onto the paper CRF or input directly into the database (i.e. REDCap). No identifiable information will be entered.

Paper CRFs will be completed in black or blue ink only and be legible. If an entry on a CRF requires change, the correction will be made by drawing a single line through the incorrect entry, followed by entering the correct data and initialing and dating the entry. Correction fluids, markers, erasures or any form of obliteration on the CRFs will not be permitted. All fields will be completed. If data are not available, a straight line will be drawn through the applicable fields and the words "None" or "N/A" will be written. The study research assistant will be responsible for entering the data into the secure, password-protected computerized REDCap database.

Collected Participant data will be audited for completeness and accuracy by the study team every 6 months (10% of records will be audited). Queries will be generated for incomplete, unreadable and/or multiple responses to single-response entries. The Data Query Form will be given to the member of the research team for correction, clarification, and signature. Data will be amended based on receipt of the signed and returned Data Query Form. The completed Data Query Form will be retained with the original completed CRF. Data queries not returned or resolved will be coded as missing values in the database.

Additional queries may be generated following a secondary review of the entered data. Once this process has been completed, and all queries have been resolved, a third (and final) review of the database will be done in preparation for analysis. Following the final review of the database, the database will be locked for the purposes of the primary analyses. Data will be de-identified and used solely for the purposes of generating aggregate datasets for analysis of the endpoints specified in the study.

10.6 Study Records Retention

Study records will be retained for 10 years after study completion. When the archiving requirements have expired, any written records associated with this study will be destroyed using confidential shredding and the electronic database used for analysis will be deleted.

10.7 Publication and Data Sharing

Data arising from this study is the property of the Sponsoring Site, but it is the function of the Study PI to disseminate information and make it available to the public. Findings from this study will be presented at national and international scientific conferences and published in peer-reviewed journals. The identity of participants will not be revealed in any published data or in presentation of the information obtained as a result of this study. This study is registered with ClinicalTrials.gov (NCT02259413) as per the requirement of the ICMJE.

De-identified data collected in this study may be shared with other researchers according to international guidelines (ICJME). Before publishing/sharing any data, it will be reviewed with the REB to ensure full compliance with privacy legislation.

De-identified participant data that underlie the results of study, will only be available to original study investigators, whose proposed use of data has been approved by the Study PI and an independent review committee for meta-analysis and to achieve the aims of the study. This de-identified data will be available following publication of the study results, with no end date. To gain access researchers will need to sign a data access and confidentiality agreement. All published data will be available ONLY in de-identified manner.

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12 APPENDICES**Appendix 1. List of Abbreviations**

Abbreviation	Definition
AE	Adverse Effect
CKD	Chronic Kidney Disease
CANN-NET	Canadian Knowledge Translation and Generation Network
CHI	Centre for Healthcare Innovation
CIHR	Canadian Institutes of Health Research
CORR	Canadian Organ Replacement Registry
CNTN	Canadian Nephrology Trials Network
ECC	End Stage Kidney Disease
ESKD	End Stage Renal Disease
DSI	Dialysis Symptom Index
EQ5D-3L	EuroQol 5 Dimension – 3 Levels
EQ-VAS	EuroQol Visual Analogue Scale
HRQOL	Health-related Quality of Life
HD	Hemodialysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
KFOC	Kidney Foundation of Canada
MRP	Manitoba Renal Program
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
RCT	Randomized Controlled Trial
SAE	Serious Adverse Effect
SD	Standard Deviation
WI	Wellness Institute

Appendix 2. Study Definitions

Early discontinuation	The study participant will be considered an “early discontinuation” in the event that they withdraw from the study during the initial 6 months of the study (withdrawal of consent, adverse effects etc.).
Intent-to-Treat sample	All randomized participants who receive the exercise intervention/standard-of-care
Lost to Follow-up	Study participants may be considered “lost to follow up” after the subject misses a minimum of 2 consecutive study visits, and the site personnel has made a number of unsuccessful phone contacts. The decision to early terminate the subject will be the decision of the PI, all attempts to establish contact with the subject will be documented in the study files.
Protocol Mandated Procedures	Any procedure performed solely for the purpose of this research study (not site-specific standard of care)
Randomized	A participant who has met all eligibility criteria; met with the study investigator or designee to discuss the study purpose, requirements (i.e. time requirements, schedule of events etc), discussed all the risks and benefits; signed the informed consent document and was randomly assigned to one of the two study groups.
Study Intervention	The investigational regimen and all protocol required therapies. This includes standardized lifestyle education, 26 weeks of cycling during HD and 26 weeks of home-based resistance exercises.
Terminated	A participant will be terminated prematurely from the study if: 1) Participant withdraws consent; Lost to follow-up, or; death.

Appendix 3. Measurement Tools

Appendix 3.1 Dialysis Symptom Index

Instructions

Below is a list of physical and emotional symptoms that people on dialysis may have. For each symptom, please indicate if you had the symptom during the past week by circling “yes” or “no.” If “yes”, please indicate how much that symptom bothered you by circling the appropriate number.

<i>During the past week: Did you experience this symptom?</i>		<i>If “yes”: How much did it <u>bother</u> you?</i>				
		<i>Not At All</i>	<i>A Little Bit</i>	<i>Some- what</i>	<i>Quite a Bit</i>	<i>Very Much</i>
1. Constipation	NO					
	YES →	1	2	3	4	5
2. Nausea	NO					
	YES →	1	2	3	4	5
3. Vomiting	NO					
	YES →	1	2	3	4	5
4. Diarrhea	NO					
	YES →	1	2	3	4	5
5. Decreased appetite	NO					
	YES →	1	2	3	4	5
6. Muscle cramps	NO					
	YES →	1	2	3	4	5
7. Swelling in legs	NO					
	YES →	1	2	3	4	5
8. Shortness of breath	NO					
	YES →	1	2	3	4	5
9. Lightheadedness or dizziness	NO					
	YES →	1	2	3	4	5
10. Restless legs or difficulty keeping legs still	NO					
	YES →	1	2	3	4	5

<i>During the past week: Did you experience this symptom?</i>		<i>If “yes”: How much did it <u>bother</u> you?</i>				
		Not At All	A Little Bit	Some- what	Quite a Bit	Very Much
11. Numbness or tingling in feet	NO					
	YES →	1	2	3	4	5
12. Feeling tired or lack of energy	NO					
	YES →	1	2	3	4	5
13. Cough	NO					
	YES →	1	2	3	4	5
14. Dry mouth	NO					
	YES →	1	2	3	4	5
15. Bone or joint pain	NO					
	YES →	1	2	3	4	5
16. Chest pain	NO					
	YES →	1	2	3	4	5
17. Headache	NO					
	YES →	1	2	3	4	5
18. Muscle soreness	NO					
	YES →	1	2	3	4	5
19. Difficulty concentrating	NO					
	YES →	1	2	3	4	5
20. Dry skin	NO					
	YES →	1	2	3	4	5
21. Itching	NO					
	YES →	1	2	3	4	5
22. Worrying	NO					
	YES →	1	2	3	4	5

During the past week: Did you experience this symptom?			<i>If “yes”: How much did it <u>bother</u> you?</i>				
			Not At All	A Little Bit	Some -what	Quite a Bit	Very Much
23. Feeling nervous	NO						
	YES →	1	2	3	4	5	
24. Trouble falling asleep	NO						
	YES →	1	2	3	4	5	
25. Trouble staying asleep	NO						
	YES →	1	2	3	4	5	
26. Feeling irritable	NO						
	YES →	1	2	3	4	5	
27. Feeling sad	NO						
	YES →	1	2	3	4	5	
28. Feeling anxious	NO						
	YES →	1	2	3	4	5	
29. Decreased interest in sex	NO						
	YES →	1	2	3	4	5	
30. Difficulty becoming sexually aroused	NO						
	YES →	1	2	3	4	5	

Appendix 3.2 EuroQol 5D-5L Health-Related Quality of Life Questionnaire



Health Questionnaire

English version for Canada

Canada (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

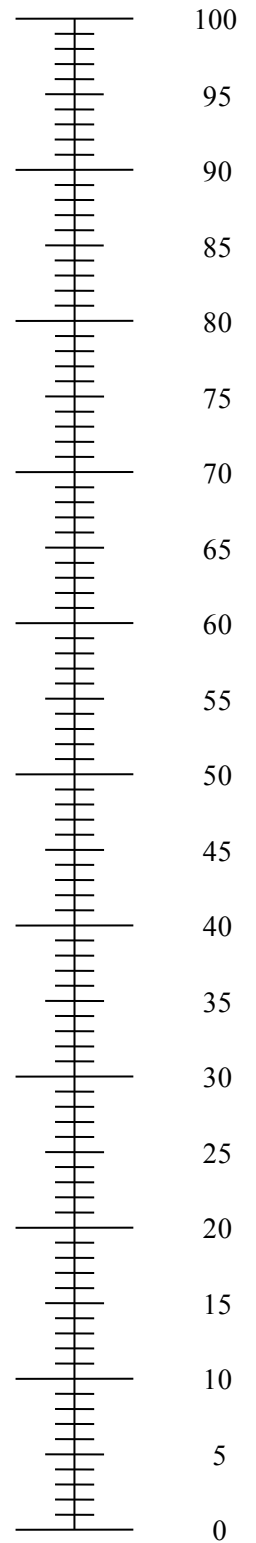
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

The best health
you can imagine



YOUR HEALTH TODAY =

The worst health
you can imagine

Appendix 3.3: Godin Leisure-Time Exercise Questionnaire

INSTRUCTIONS

In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively. Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

$$\text{Weekly leisure activity score} = (9 \times \text{Strenuous}) + (5 \times \text{Moderate}) + (3 \times \text{Light})$$

The second question is used to calculate the frequency of weekly leisure-time activities pursued “long enough to work up a sweat” (see questionnaire).

EXAMPLE

$$\text{Strenuous} = 3 \text{ times/wk}$$

$$\text{Moderate} = 6 \text{ times/wk}$$

$$\text{Light} = 14 \text{ times/wk}$$

$$\text{Total leisure activity score} = (9 \times 3) + (5 \times 6) + (3 \times 14) = 27 + 30 + 42 = 99$$

Godin, G., Shephard, R. J.. (1997) [Godin Leisure-Time Exercise Questionnaire](#). Medicine and Science in Sports and Exercise. 29 June Supplement: S36-S38.

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY)

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE (NOT EXHAUSTING)

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE (MINIMAL EFFORT)

(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

Times Per Week

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN

1. 👉

SOMETIMES

2. 👉

NEVER/RARELY

3. 👉

Appendix 3.4 Shuttle Walk Test Protocol

The Shuttle Walking Test (SWT) is an objective, reproducible measure of functional capacity. It was originally designed for use in patients with chronic obstructive pulmonary disorders and has been found to be a reproducible and valid outcome measure (Singh et al, 1992, 1994).

It has been used for patients attending Pulmonary Rehabilitation as a means of:

1. determining appropriate exercise intensity for individuals
2. identifying an appropriate home walking programme
3. measuring changes in functional capacity pre-and post-training.

The test is usually carried out by a Chartered Physiotherapist and, before testing, a thorough assessment of the patient is needed to ensure the relevance and safety of testing.

Criteria	✓
Blood pressure adequately controlled SBP < 180 mm Hg	
No angina at rest/unrelated to exertion	
Subject has taken all prescribed medication	
Subject free from sore throat, a cold or other temporary illness	
No orthopaedic problems that would be exacerbated by exercise	
Testing being done ideally at least 2 hours after subject has eaten meal	
Resting pulse regular and less than 100 bpm	
If subject diabetic, no hypoglycaemic episodes in past week	
No strenuous physical activity on day of testing	
Subject has suitable clothing/footwear	
Subject gives informed consent (verbal)	
Tester competent in basic life support	
Access to telephone in emergency	

Table 1 Pre-Test Checklist for Shuttle Walking Test

The test itself is a scaled down version of a Bleep Test (Leger and Lambert, 1982) which involves walking around a course identified by two cones (see fig1).

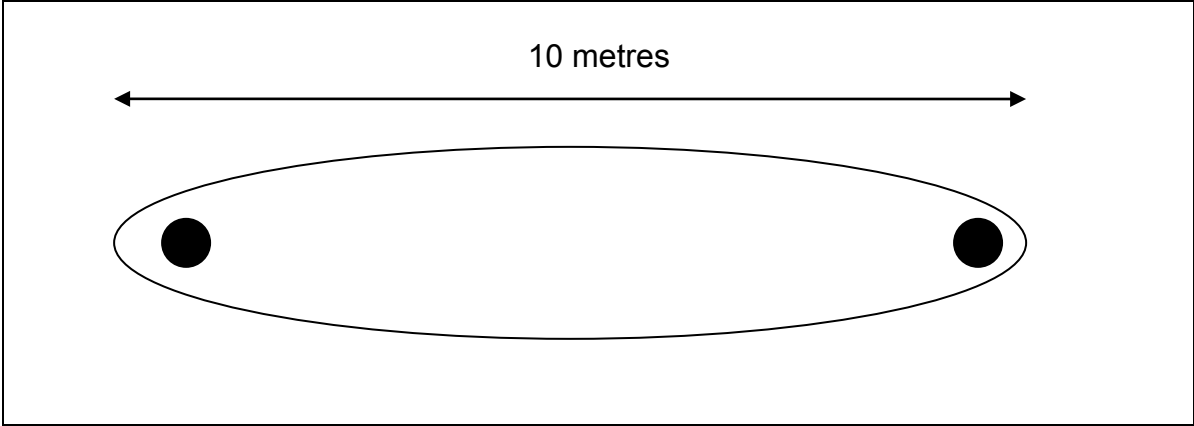


Figure 1 Plan of Shuttle Walk Test course

The walking speed is externally paced and increases each minute (see Table 2).

LEVEL	SPEED	
	mph	kmph
1	1.12	1.8
2	1.5	2.4
3	1.88	3.0
4	1.26	3.6
5	2.64	4.3
6	3.02	4.9
7	3.4	5.5
8	3.78	6.1
9	4.16	6.7
10	4.54	7.3
11	4.92	7.9
12	5.3	8.5

Table 2 Shuttle Walking Test

It is important to know what limits a patient’s exercise tolerance and so the test is ‘symptom-limited’. In other words subjects are asked to keep going until they develop symptoms and are unable to continue with the test (e.g. leg fatigue, breathlessness).

Subject unable to keep up with set pace; the set pace is defined as arriving within 0.5 metres from the cone when bleep sounds
At subject's request e.g. shortness of breath, leg fatigue, pain
At operator's discretion if concerned re: subject's physical status e.g. oxygen saturation level, angina, dizziness

Table 3 Endpoints for Sub Maximal Shuttle Walking Test

The equipment needed and protocol for carrying out the test are shown in Tables 4 and 5.

Quiet, private area with non-slip surface
Minimum floor space of 15m x 3m
Shuttle Walking Test CD ¹
CD player
Stopwatch for pre-test calibration
2 cones set 9 metres apart
Pulse oximeter
Borg breathlessness and RPE scales

¹available from Department of Respiratory Medicine, University Hospitals of Leicester, Groby Road, Leicester LE3 9QP.

Table 4 Equipment needed for Sub Maximal Shuttle Walking Test

<ul style="list-style-type: none"> • Go through Pre-Test Checklist (Table 1) with subject. If answer to any response is 'No' or 'Don't Know', then do not carry out test
<ul style="list-style-type: none"> • Set marker cones 9 metres apart
<ul style="list-style-type: none"> • Fit patient with pulse oximeter
<ul style="list-style-type: none"> • Explain Borg ratings of breathlessness and perceived exertion (RPE) and ensure subjects understand how to use these
<ul style="list-style-type: none"> • Play the instructions on the CD to the patient
<ul style="list-style-type: none"> • Clarify the endpoints of the test with subject (See Table 3)
<ul style="list-style-type: none"> • Walk round with the patient for the first or two minutes to help them establish the correct pace (starting pace is approximately 1 mph)
<ul style="list-style-type: none"> • Tell subject about an increase in walking speed just prior to the next triple bleep
<ul style="list-style-type: none"> • Discourage subjects from talking while they are doing the test
<ul style="list-style-type: none"> • Record total distance walked in metres, heart rate and oxygen saturation immediately once sitting
<ul style="list-style-type: none"> • Record reason for stopping test

Table 5 Protocol for Sub Maximal Shuttle Walking Test

Note: Most exercise tests are subject to a practice effect, i.e. a second test performed soon after the first, but before any exercise training is undertaken, generally yields an improved outcome measure. It is therefore always preferable to conduct a practice walk and to use the measurement from the second walk as the 'baseline' measurement. Without this, any improvement in post-training outcome is likely to be exaggerated.

Appendix 3.5: Modified Fried Criteria

- (a) Unintentional weight loss of > 10 pounds in last year
- (b) Grip strength weakness (< 30 kg in males/< 20 kg in females (in strongest hand)
- (c) Exhaustion as determined by 2 questions from CES-D questionnaire
- (d) Slowness: established cut off for 4 metre timed walk adjusted for sex and height
- (e) Low physical activity: Godin-Shephard Leisure Time Index in lowest quintile of normative data stratified by age and sex.

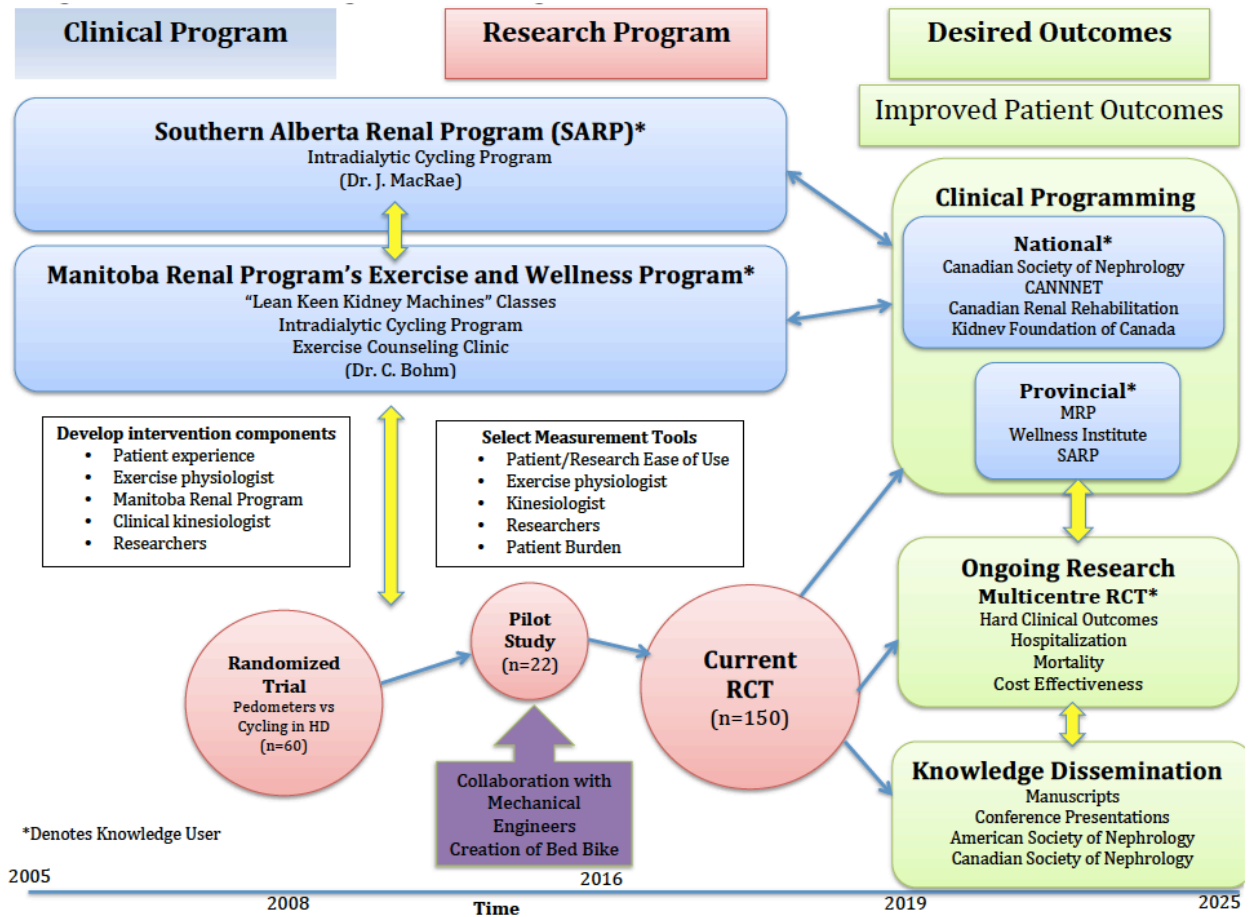
Appendix 3.6: Self-Efficacy for Exercise Survey

Self efficacy questionnaire

How confident are you right now that you could exercise three times per week for 20 minutes if:

1. The weather was bothering you?	0	1	2	3	4	5	6	7	8	9	10
2. You were bored by the program or activity?	0	1	2	3	4	5	6	7	8	9	10
3. You felt pain when exercising?	0	1	2	3	4	5	6	7	8	9	10
4. You had to exercise alone?	0	1	2	3	4	5	6	7	8	9	10
5. You did not enjoy it?	0	1	2	3	4	5	6	7	8	9	10
6. You were too busy with other activities?	0	1	2	3	4	5	6	7	8	9	10
7. You felt tired?	0	1	2	3	4	5	6	7	8	9	10
8. You felt stressed?	0	1	2	3	4	5	6	7	8	9	10
9. You felt depressed?	0	1	2	3	4	5	6	7	8	9	10

Appendix 4: Knowledge Translation Strategy



Appendix 5: COVID-19 Assessment Procedure

Renal Rehab Assessment COVID-19 Operating Procedure

- Participants only on intervention for 1 month will be approached to re-start the entire study again at HSC and SOGH (completed Mar 16, 2020)
- Controls continue
- No active participants currently at SBGH

Study Recruitment:

- On hold until future

Activity Logs

- Will be collected by Eric and Krista (study kinesiologists) by phone or email following the timeline of the protocol

Baseline Assessments:

- On hold until future

Assessments 2-4

- **Questionnaires** (DSI, Self Efficacy, EQ-5D-5L, Godin-Shephard Physical Activity) will be either:
 - Conducted over the phone (Eric or Krista will phone participants)
 - Emailed to participants to be filled out and emailed back (emailed by Eric or Krista)
 - Mailed to participants with a postage-paid envelope for return to CDIC (mailed by Eric or Krista)
- Recovery time, hospitalization since last assessment, exhaustion, and weight loss questions should still be asked
- **Accelerometers**
 - Will not be sent out via mail to participants to avoid potential transmission of COVID-19
 - Accelerometer data will not be collected at this time
- **Participant Reimbursement**
 - When assessments are completed the participant will be mailed a \$25 VISA/Mastercard gift card and a signature page with a postage-paid envelope for return
 - This envelope should be addressed to be returned to CDIC
 - Monica (research coordinator) will be mailing the gift cards out from home
 - Participant addresses will be emailed to her over the secure WRHA email in a password protected document and deleted once letter addressed

- Signature pages will be collected in CDIC and given to Krista to compile and determine if a participant needs to be contacted again
- **Physical Tests** (Shuttle Walk, Gait Speed, Hand Grip Strength)
 - Unable to be completed at this time
- **Clinical Outcomes Data Collection** (chart reviews)
 - Chart reviews for assessments conducted after March 16th will be completed once research staff are able to return to work on dialysis units

Site Specific Procedure

Sherbrook Dialysis Unit (Eric still required to report to work for clinical component of his position as per Manitoba Renal Program)

1. Call participant a week before scheduled assessment to select a time that works for them
2. Call participant day of assessment at chosen time and go over questions and questionnaires
3. Tell participant to expect \$20 in an envelope given to them by a nurse and a signature page for them to sign
4. Call participant to confirm receiving \$20 and to remind them to return the signature page to their HD nurse who will drop this envelope off in Eric's SCDU office mailbox
5. Confirm that signature sheet was returned signed and dated with Clara or Krista

Health Sciences Centre Dialysis Units (CDU, PHDU, GG7) and Seven Oaks Units

1. Call participant a week before scheduled assessment to select a time that works for them
2. Call participant day of assessment at chosen time and go over questions and questionnaires
3. Tell participant to expect a \$25 gift card in the mail along with a signature page and a postage-paid envelope
4. Mail out gift card to participant with signature page and a return postage-paid envelope once assessment is complete

5. Call participant to confirm receiving the gift card and to remind them to return the signed signature page via mail to CDIC
6. Confirm that signature page was returned signed and dated with Clara or Krista

St. Boniface Dialysis Units

No active participants

* Mail option will be given to participants who do not want to or are unable to complete the questionnaires via phone or email.